Du *et al. Reproductive Biology and Endocrinology* (2025) 23:129
https://doi.org/10.1186/s12958-025-01465-1

Reproductive Biology and Endocrinology

REVIEW Open Access

Hydrogen sulfide in placental development and pregnancy disorders: mechanisms, therapeutic potential, and translational challenges

Lijia Du[1†], Rui Zheng[1†], Weina Ren[1], Yingru Liu[1], Xiaoxiong Zhu[1], Shiyang Chang[2*] and Zhifen Yang[1*]

Abstract

The placenta plays a crucial role in maintaining pregnancy stability, regulating fetal growth, and facilitating maternal–fetal exchange. Its proper development relies on placental vasculogenesis and angiogenesis, along with adaptive remodeling of the maternal uterine vasculature. However, the mechanisms underlying placental development and the successful establishment of the maternal–fetal interface remain incompletely understood. As the third gaseous signaling molecule identified after nitric oxide (NO) and carbon monoxide (CO), hydrogen sulfide (H_2S) has been demonstrated to regulate vascular adaptation during pregnancy by promoting angiogenesis and neovascularization. Dysregulated H_2S biosynthesis has been implicated in pregnancy complications, including preeclampsia (PE), fetal growth restriction (FGR), and preterm birth (PTB), underscoring its potential as a therapeutic target. Recent studies have revealed that H_2S regulates placental function via multiple signaling pathways, including activating adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channels, large-conductance calcium-activated potassium channels (BK_{Ca} channels), endothelial nitric oxide synthase (eNOS) signaling, and mitochondrial dynamics. Notably, H_2S-mediated persulfidation of mitochondrial Rho GTPase 2 (Miro2) has been shown to maintain trophoblast invasiveness and promote placental vascular homeostasis. Additionally, exogenous H_2S donors (e.g., GYY4137 and NaHS) have demonstrated therapeutic potential in experimental models, effectively reversing PE-like pathologies, improving placental perfusion, and restoring trophoblast function. Research further indicates that BK_{Ca} channels play a key role in H_2S-mediated vasodilation by modulating intracellular Ca^{2+} flux, which influences placental vascular tone and perfusion, reinforcing the importance of H_2S in maternal–fetal circulation regulation. This review provides a comprehensive summary of H_2S biosynthesis and metabolism and its regulatory role in early placental development. Notably, elevated estrogen levels during pregnancy have been identified as key regulators of H_2S production, and we discuss the molecular mechanisms by which estrogen modulates H_2S synthesis. Furthermore, we discuss the vascular-protective and anti-inflammatory properties of H_2S

†Lijia Du and Rui Zheng contributed equally to this work.

*Correspondence:
Shiyang Chang
18901410@hebmu.edu.cn
Zhifen Yang
cxsxfy@126.com

Full list of author information is available at the end of the article

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Sulfatonic®

donors and dual-donor strategies. As research continues to reveal H_2S-mediated mechanisms in placental function and pregnancy disorders, optimizing the pharmacological application and clinical translation of H_2S donors and combination therapies will be a key research focus. Advancing H_2S metabolic regulation, signaling pathways, and targeted delivery systems may drive the development of novel diagnostic tools and therapeutic strategies for pregnancy complications.

Keywords Hydrogen sulfide (H_2S), Placental development, Spiral artery remodeling (SAR), Uterine blood flow (UtBF), H_2S donors, Estradiol-β, Preeclampsia (PE), Fetal growth restriction (FGR)

Introduction

During pregnancy, the placenta plays a pivotal role in maintaining maternal–fetal homeostasis by regulating nutrient and gas exchange, hormone secretion, and immune tolerance at the maternal–fetal interface [1, 2]. Its proper development relies on placental vasculogenesis and angiogenesis, as well as the adaptive remodeling of maternal uterine vasculature [3–5]. However, the placenta lacks intrinsic vascular regulation, and its perfusion relies on dynamic maternal hemodynamic changes, especially in the uterine arteries (UAs) [5, 6]. A key process in placental vascular adaptation is spiral artery remodeling (SAR), which is initiated by extravillous trophoblast (EVT) invasion and completed through endothelial and smooth muscle cell (SMC) replacement and vascular dilation [7–10]. This remodeling process creates a high-capacity, low-resistance circulatory bed critical for optimal fetal perfusion [11–14] (Fig. 1). Abnormal EVT invasion and inadequate SAR are strongly associated with major pregnancy complications, including preeclampsia (PE) [15–18], fetal growth restriction (FGR) [19–21], recurrent spontaneous abortion (RSA) [22–24], and preterm birth (PTB) [25], all of which can affect long-term maternal and fetal health [26–29].

Recent genetic studies suggest that placental dysfunction is often underrecognized as a primary cause of congenital anomalies. Mouse models have shown that embryo lethality caused by certain gene deletions can be rescued by functional placentas, indicating that the placenta may play a decisive role in fetal survival and organogenesis [30–35]. For example, mutations in Pparg- and Mapk14 (p38α)-mutant have been linked to cardiac malformations secondary to placental defects [36, 37]. Clinical studies further support a strong association between placental abnormalities and neonatal neurodevelopmental disorders [38–45]. These findings underscore the need to understand the molecular signals that govern placental vascular function and remodeling. Among emerging molecular regulators, hydrogen sulfide (H_2S) has attracted growing interest. Recognized as the third gasotransmitter [46] following nitric oxide (NO) [47] and carbon monoxide (CO) [48]. H_2S exerts diverse effects on vascular biology, including vasodilation, angiogenesis, anti-inflammation, and antioxidant defense [49–54]. In the context of pregnancy, H_2S enhances uteroplacental blood flow by activating adenosine triphosphate (ATP)-sensitive K+ (K_{ATP}) and large-conductance calcium-activated potassium (BK_{Ca}) channels [51–54], potentiating NO-mediated vasodilation [55, 56], and modulating EVT invasion and vascular endothelial growth factor (VEGF)-driven angiogenesis [49, 57, 58]. Notably, it maintains placental vascular homeostasis even in pathological conditions such as PE and FGR. Despite its promising vascular-protective potential, the precise roles and regulatory mechanisms of H_2S in placental development remain incompletely defined. Questions persist regarding how H_2S modulates trophoblast behavior, SAR, and local hemodynamics during early pregnancy. Moreover, the interplay between H_2S and estrogen, a key hormone elevated during pregnancy, may offer additional insight into H_2S biosynthesis and action within the uteroplacental environment.

Given that many pregnancy complications such as PE, FGR, PTB, and placenta accreta originate in early placentation but typically manifest later in gestation [59, 60], understanding early molecular disruptions is crucial for advancing predictive and therapeutic strategies. This review aims to comprehensively summarize the emerging roles of H_2S in placental physiology, including its effects on vascular remodeling, trophoblast function, oxidative stress, and immune regulation. We further discuss the regulation of H_2S biosynthesis by estrogen and the therapeutic potential of H_2S donors, highlighting future directions for clinical translation.

H_2S biosynthesis and mechanisms

Historical background and significance of H_2S

H_2S was historically viewed as a toxic gas, primarily due to its inhibitory effects on mitochondrial respiration at high concentrations. However, research in the mid-20th century revealed its endogenous production in mammals, challenging the traditional toxicological paradigm [61, 62]. In 1996, Hideo Kimura identified H_2S as neuromodulator synthesized in the brain and proposed its role as a signaling molecule [63]. This discovery, followed by studies demonstrating H_2S-induced vasodilation and anti-inflammatory activity, laid the foundation for its recognition as the third endogenous gasotransmitter alongside NO and CO [46, 64, 65]. Additionally, H_2S plays crucial regulatory roles in both male and female

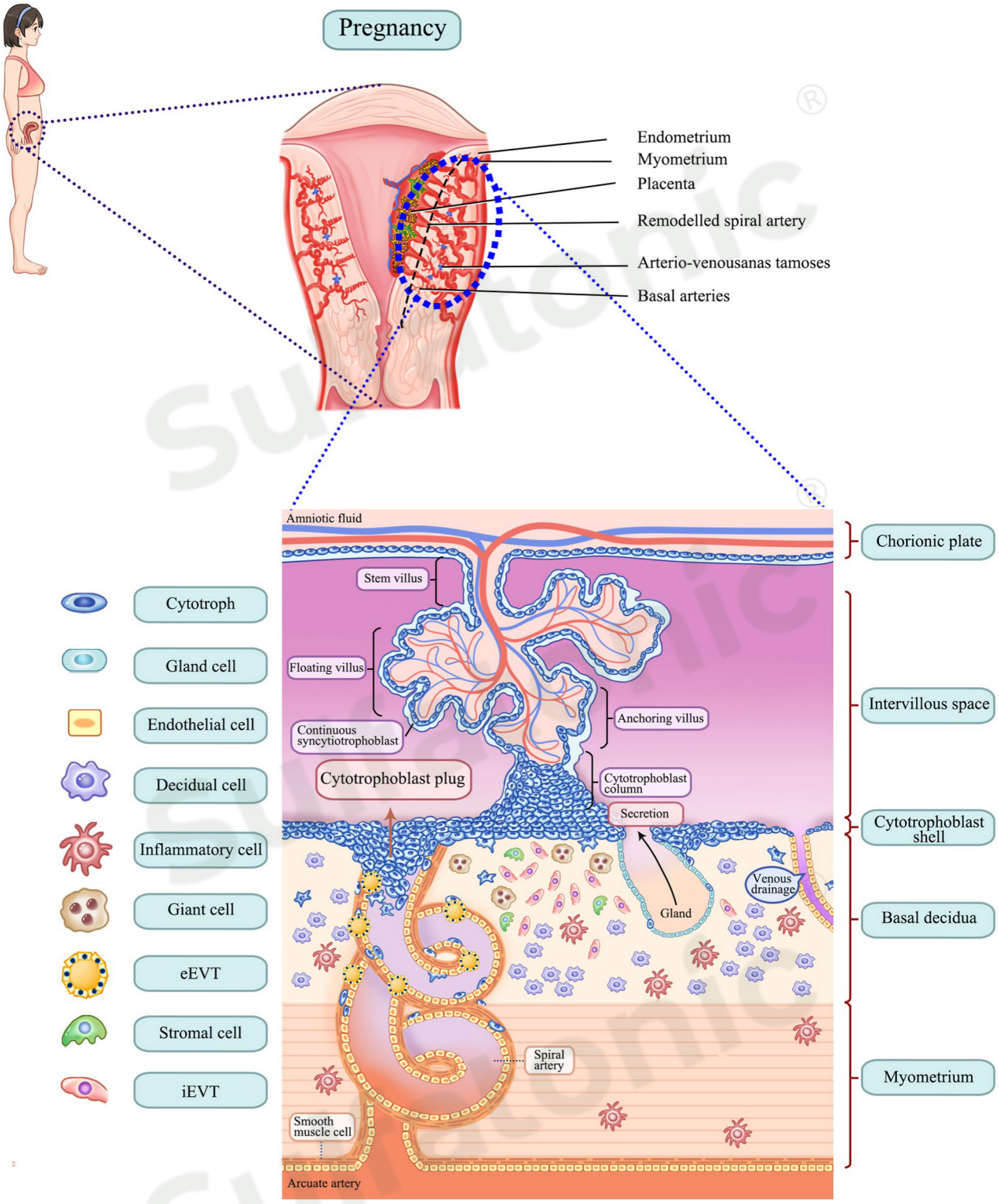


Fig. 1 Maternal-Fetal Interface During Early Placental Development. In early pregnancy, EVTs originating from the cytotrophoblast shell invade the maternal decidua and SAs, orchestrating essential vascular remodeling. iEVTs infiltrate the decidual stroma, while eEVTs migrate into the SA lumen, progressively replacing endothelial cells and inducing VSMC degradation. This transformation converts the tightly coiled, high-resistance SAs into widened, low-resistance vessels, optimizing maternal blood flow to the placenta and sustaining fetal development. Notes: EVTs: extravillous trophoblasts; iEVTs: interstitial EVTs; eEVTs: endovascular EVTs; SA: spiral Arteries; VSMC: vascular smooth muscle cell

Sulfatonic®

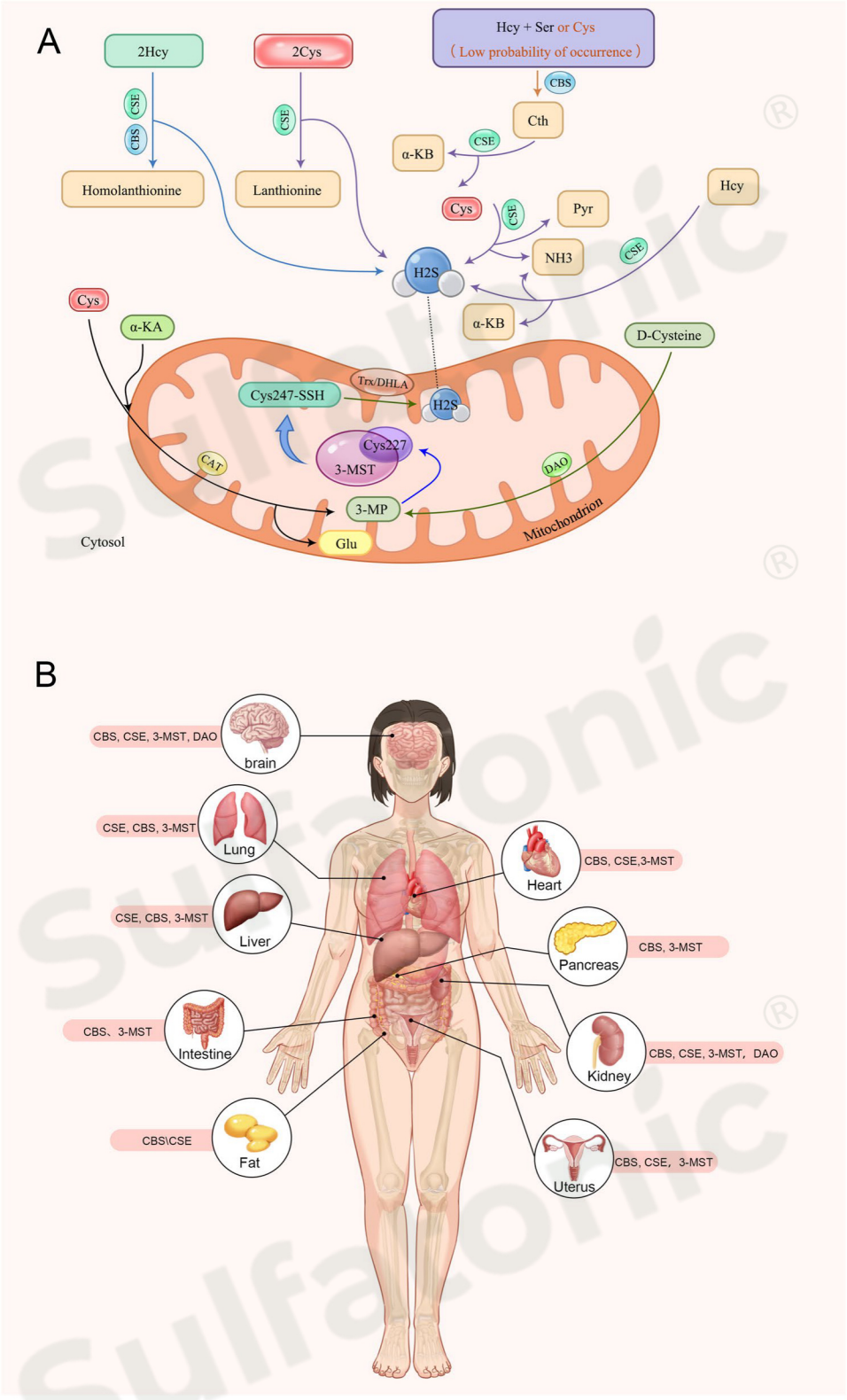


Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Biosynthesis of H_2S and tissue distribution of key enzymes (CBS, CSE, and 3-MST). **A** H_2S biosynthesis pathways. H_2S is synthesized through three key enzymes: CBS, CSE, and3-MST. CBS catalyzes the conversion of Hcy and Ser into Cth, which is further degraded by CSE to produce Cys and H_2S. CBS can also generate H_2S by catalyzing Hcy condensation or using Cys as a substrate. CSE produces H_2S through cystathionine degradation and alternative reactions involving L-cysteine or homocysteine, leading to the formation of lanthionine, homolanthionine, pyruvate, α-KB, and H_2S. 3-MST converts 3-MP, derived from L-cysteine via CAT, into a persulfide intermediate, which is reduced to release H_2S. Additionally, 3-MP can undergo non-enzymatic degradation to form H_2S. DAO also contributes to H_2S production by converting D-cysteine into 3-MP, particularly in the kidney and cerebellum. **B** Tissue distribution of CBS, CSE, and 3-MST. The expression patterns of these enzymes vary across different organs. Notes: CBS: Cystathionine β-Synthase; CSE: Cystathionine γ-Lyase; CAT: Catalase; DAO: D-Amino Acid Oxidase; 3-MST: 3-Mercaptopyruvate Sulfurtransferase; 3MP: 3-Mercaptopyruvate; α-KB: α-Ketobutyrate; Pyr: Pyruvate; Cys: L-cysteine; Hcy: Homocysteine; Ser: Serine; α-KA: α-Keto Acid; Cth: Cystathionine ; Glu: Glutamate; -SSH: Persulfide; Trx: Thioredoxin; DHLA: Dihydrolipoic Acid

reproductive systems and pregnancy [66–69], supporting processes such as oocyte maturation, corpus luteum maintenance, sperm production and motility, trophoblast invasion, and placental blood flow optimization. These functions collectively ensure normal reproductive processes and healthy pregnancy progression.

Biosynthesis and metabolic pathways of H_2S

The synthesis and metabolism of H_2S in vivo involve a complex interplay of enzymatic and nonenzymatic pathways. Its biosynthesis occurs through enzymatic reactions, while its degradation involves oxidation, methylation, binding to methemoglobin, and exhalation in a gaseous form.

Enzymatic pathways of H_2S synthesis

H_2S is primarily synthesized by three key enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST). These enzymes collectively regulate H_2S production through interrelated metabolic pathways and function in specific physiological environments, including the uterus, placenta, ovaries, embryonic development, and pregnancy maintenance [69] (Fig. 2). CBS/CSE-H_2S systems are expressed in the UA across species such as sheep [70], rats, and humans [71], suggesting a potential role in uterine blood flow (UtBF) regulation.

CBS, encoded on chromosome 21, is a pyridoxal-5'-phosphate (PLP)-dependent enzyme and the first in the transsulfuration pathway. It catalyzes the conversion of homocysteine (Hcy) and serine (Ser) or cysteine to cystathionine (Cth) and H_2S [63, 72–77]. CBS is highly expressed in the central nervous system, liver, gastrointestinal tract, placenta, and uterine vasculature, where it supports placental angiogenesis and fetal perfusion via H_2S-mediated signaling involving VEGF, placental growth factor (PlGF), and mitogen-activated protein kinases (MAPK) pathways [68, 70, 71, 78, 79]. During pregnancy, CBS expression is upregulated in both the placenta and UA [70, 71], and its dysregulation is implicated in pathologies such as Down syndrome [80–82]. Knockout mouse models reveal that CBS deficiency impairs placental growth, uterine weight, and follicular maturation, with disrupted estrous cycles and reduced conception rates, highlighting its importance in maintaining a supportive reproductive environment [83–87]. Beyond H_2S synthesis, CBS can also produce NO or peroxynitrite ($ONOO^-$) through interactions with substrates like nitrite (NO_2^-), implicating its role in vascular tone regulation and oxidative stress balance [88].

CSE, encoded on chromosome 1, is another PLP-dependent enzyme predominantly expressed in the cardiovascular system, respiratory system, kidneys, liver, uterus, and peripheral tissues [89–91]. CSE is highly expressed in the cytoplasm but can translocate to mitochondria under specific conditions [92]. It catalyzes H_2S production from Cth or cysteine via multiple β- or γ-cleavage reactions [76, 93–95]. While CBS is estrogen-sensitive and dynamically expressed during pregnancy, CSE expression remains relatively stable [70, 71]. CSE-knockout mice show vascular dysfunction, decreased serum H_2S, and impaired pregnancy outcomes, including reduced implantation success and increased fetal inflammation, suggesting roles in maternal vascular adaptation and anti-inflammatory regulation [84, 96].

3-MST, encoded on chromosome 22, is a non-PLP-dependent mitochondrial enzyme that uses 3-mercaptopyruvate (3-MP) as substrate, with cysteine aminotransferase (CAT) and dihydrolipoic acid as cofactors [86, 97–102]. It is widely distributed in the liver, kidneys, testes, brain, and endocrine organs, whereas lower levels are found in the spleen, thymus, lungs, and intestines [98, 99]. It catalyzes the formation of persulfides (–SSH) and contributes to redox regulation and mitochondrial H_2S reservoirs [102–105]. While 3-MST and its partner enzyme CAT are expressed in UA, their expression levels remain unchanged throughout the menstrual cycle and pregnancy [71].Of note, a fourth enzyme D-amino acid oxidase (DAO), can generate 3-MP from D-cysteine, which is subsequently processed by 3-MST/CAT to produce H_2S. This pathway is highly expressed in the kidneys and cerebellum, with studies indicating that D-cysteine generates H_2S approximately 60 times more efficiently than L-cysteine (Cys) does [106], making it a potential therapeutic strategy for targeted H_2S delivery in these organs. However, DAO expression in vascular cells remains unreported.

Microbial and dietary sources of H_2S: enzymatic and nonenzymatic pathways

Beyond endogenous enzymatic synthesis, gut microbiota, diet, and nonenzymatic chemical reactions provide significant contributions to systemic H_2S production, particularly in the gastrointestinal and circulatory systems. These sources work synergistically under physiological and pathological conditions to maintain H_2S homeostasis and expand its biological functionality.

The gut microbiota represents a significant source of H_2S, which is generated through both enzymatic and nonenzymatic mechanisms. Sulfate-reducing bacteria (SRB), such as *Desulfotomaculum*, *Desulfovibrio*, and *Desulfobacter* [107], dominate the anaerobic colonic environment, utilizing sulfate (SO_4^{2-}) as a terminal electron acceptor to produce sulfide (S^{2-}), which subsequently converts to H_2S under acidic conditions [108]. In addition, non-SRB taxa including *Escherichia coli*, *Salmonella enterica*, and *Clostridium* species, generate H_2S via Cys metabolism through Cys desulfhydrase [109, 110]. Some gut-resident bacteria such as *Staphylococcus* and *Enterobacter* generate sulfite (SO_3^{2-}) or thiosulfate ($S_2O_3^{2-}$), which can undergo nonenzymatic reduction to produce H_2S [111, 112].

Dietary sulfur compounds also contribute to H_2S availability. Enzymatically, cruciferous vegetables (e.g., mustard greens, Chinese kale, and broccoli) are rich in isothiocyanates and glucosinolates, which are metabolized in the gut to release H_2S [113]. Garlic-derived organosulfur compounds such as diallyl trisulfide (DATS) can release H_2S through thiol-disulfide exchange reactions with glutathione (GSH), also modulating cellular redox status [113–116]. Recent evidence suggests that nonenzymatic H_2S formation can also occur in peripheral tissues via interactions between cysteine and diet-derived ferric iron (Fe^{3+}) [117] and PLP, the active form of vitamin B6 [117, 118]. These reactions are promoted under oxidative stress, particularly in the lungs, heart, and spleen, and may serve as compensatory mechanisms for maintaining local H_2S levels when enzymatic activity is impaired.

Recent studies have shown that certain dietary sulfur compounds can modulate mammalian signaling pathways by releasing H_2S, which plays essential roles in cardiovascular, gastrointestinal, neural, and immune functions. Reduced H_2S levels are associated with disorders such as hypertension, diabetes, and immune dysregulation [119]. Meat-derived proteins serve as key substrates for microbial H_2S production in the colon [120]. Once absorbed into the intestinal circulation, H_2S can act on blood vessels, activate enteric neurons, and influence systemic blood pressure regulation [121]. Additionally, long-term adherence to sulfur-rich dietary patterns has been linked to increased risk of distal colorectal cancer [122], likely mediated by sulfur-metabolizing bacteria. These findings highlight the systemic impact of diet–microbiota–H_2S interactions and their potential relevance to maternal and placental health.

In summary, these microbial, dietary, and endogenous metabolism form an interconnected network, which complements enzymatic pathways and contributes to immune modulation, vascular regulation, and oxidative homeostasis—processes highly relevant in pregnancy. Under hypoxic or inflammatory conditions, such as those seen in placental insufficiency or gestational disorders, these alternative sources may become particularly active and influence maternal-fetal adaptation.

Metabolic pathways of H_2S

To maintain physiological H_2S homeostasis, biological systems use three primary metabolic pathways to eliminate or degrade H_2S, ensuring that H_2S levels remain within physiological limits and preventing its accumulation. These pathways include the mitochondrial enzymatic sulfide oxidation pathway, the cytosolic methylation pathway, and the heme-dependent sulfide oxidation pathway [93].

Mitochondrial enzymatic oxidation: the primary clearance route Within mitochondria, H_2S is oxidized by sulfide quinone oxidoreductase (SQR) into protein-bound -SSH [123, 124], with released electrons entering the electron transport chain, linking H_2S metabolism to cellular respiration and energy production [125, 126]. Subsequent oxidation involves persulfide dioxygenase (ETHE1) and sulfite oxidase (SUOX), producing sulfate (SO_4^{2-}) for urine excretion [127–129]. However, when SO_3^{2-} accumulates beyond the metabolic capacity of SUOX, some SO_3^{2-} reacts with -SSH via thiosulfate sulfurtransferase (TST), forming thiosulfate ($S_2O_3^{2-}$) [76, 113, 130], which serves as a reversible H_2S storage form, releasing H_2S when needed. Tissue-specific variations exist: the liver favors SO_4^{2-} generation, kidneys produce both $S_2O_3^{2-}$ and SO_4^{2-}, and colonic epithelial cells—constantly exposed to microbially derived H_2S—exhibit high SQR and TST expression to rapidly oxidize and buffer excess H_2S [93, 131]. This pathway not only detoxifies H_2S but also integrates redox and energy homeostasis.

Cytosolic methylation: a secondary backup In the cytoplasm, thiol S-methyltransferase catalyzes H_2S methylation using S-adenosylmethionine to generate methanethiol (CH_3SH). CH_3SH can then be further converted into thiocyanate or dimethyl sulfide for excretion via urine or exhalation [93, 113, 127, 131]. Although the methylation pathway contributes to H_2S metabolism, its physiological significance is relatively

minor compared with that of mitochondrial oxidation. Studies suggest that under low H_2S conditions, methylation may be enhanced to assist in H_2S clearance, whereas when H_2S levels exceed physiological thresholds, mitochondrial oxidation remains the predominant degradation mechanism to maintain homeostasis [113].

Heme-dependent oxidation: a buffering and regulatory mechanism In plasma, H_2S binds to deoxyhemoglobin forming sulf-hemoglobin (S-Hb), reducing free H_2S toxicity and releasing it in response to fluctuating blood oxygen levels [132, 133]. Under oxidative conditions, methemoglobin or Fe^{3+} mediates H_2S oxidation to $S_2O_3^{2-}$ and polysulfides ($HSxS^-$) [134–136], which serve as temporary reservoirs or signaling molecules. $S_2O_3^{2-}$ primarily serves as an intermediate in H_2S oxidation, eventually converting to SO_4^{2-} and excreted in the urine. Under specific conditions, it may also function as a reversible storage form of H_2S. Moreover, $HSxS^-$, a byproduct of H_2S oxidation, can serve as a temporary H_2S reservoir and be cleared through renal, pulmonary, or metabolic pathways [137–139]. This mechanism not only buffers systemic H_2S fluctuations but also modulates vascular tone, especially relevant in pregnancy, where H_2S influences uteroplacental blood flow, fetal lung development, and hypoxic adaptation [93, 140–142].

H_2S metabolism involves both irreversible degradation and reversible storage-release cycles, forming a homeostatic buffering system. Under oxidative stress or hypoxia, thiosulfate and $HSxS^-$ may regenerate H_2S, contributing to vascular protection, redox signaling, and metabolic adaptation. Importantly, dysregulated H_2S metabolism is implicated in diverse pathologies, including mitochondrial dysfunction (such as ETHE1 deficiency leading to excessive H_2S accumulation) [129, 140], cardiovascular diseases (H_2S metabolism abnormalities contributing to hypertension and atherosclerosis), and inflammatory disorders (both H_2S excess and deficiency affecting immune regulation) [86, 143]. H_2S metabolism may also be closely linked to pregnancy-related complications, where elevated Hcy may interfere with H_2S production and contribute to PE, RSA, elevated uterine arterial resistance, and fetal congenital anomalies [144–146]. Excessive H_2S may inhibit mitochondrial cytochrome c oxidase, impairing energy metabolism [147]. While H_2S exerts diverse physiological effects across multiple organ systems, this review centers on its roles in placental development and pregnancy-related pathologies, with systemic functions discussed only insofar as they contribute to maternal-fetal health.

The role of H_2S in pregnancy-associated vascular adaptation and placental function

Successful placental development depends on the intricate interactions between fetal trophoblasts and the maternal decidua, particularly the differentiation of trophoblasts and remodeling of uterine vasculature. During early pregnancy, cytotrophoblasts (CTBs) give rise to syncytiotrophoblasts (STBs) for nutrient exchange, and EVTs, which invade the decidua and drive SAR [8, 148]. SAR is a critical process for uterine vascular adaptation during pregnancy, whereby eEVTs invade the vascular lumen, replace endothelial cells (ECs), and restructure the vessel wall [9, 149]. Immune cells such as macrophages and uterine natural killer (uNK) cells assist by releasing matrix metalloproteinases (MMPs) and proangiogenic signals [9]. In early gestation, EVT plugs transiently block maternal red blood cell entry into the intervillous space. Imaging studies, such as ultrafast functional photoacoustic microscopy, reveal that this hypoxic environment supports vascular expansion and placental development until maternal blood flow is fully established by 10–12 weeks [150–153]. Meanwhile, UAs and other branches undergo structural adaptation, with UtBF increasing up to 50-fold in late pregnancy [154, 155]. However, UA hemodynamic abnormalities or inadequate SAR can lead to restricted placental perfusion, contributing to pregnancy complications such as FGR [21, 156], PE [15, 157], stillbirth, and RSA [12]. Gasotransmitters such as H_2S, NO, and CO are increasingly recognized as key regulators of placental vascular adaptation. H_2S, in particular, promotes uterine and placental vasodilation, supports trophoblast function, reduces oxidative stress, and modulates inflammation [158]. The following sections focus on the molecular mechanisms by which H_2S contributes to vascular regulation, trophoblast function, UA dilation, and oxidative stress/inflammation modulation, offering insights into potential therapeutic targets for pregnancy-related disorders.

The role of H_2S in placental vascular regulation and trophoblast function

Normal placental development relies on trophoblast proliferation, migration, and invasion, which are essential for successful embryo implantation and maternal–fetal vascular remodeling. H_2S is increasingly recognized as a key modulator of these processes, not only by supporting trophoblast function but also by regulating vascular tone within the placental circulation. Mohammed et al. [159]. reported vessel-specific responses to H_2S in human placental vasculature: while H_2S did not induce vasodilation in human umbilical arteries and instead triggered mild contraction via inhibition of the NO/soluble guanylate cyclase (sGC) signaling pathway, it caused vasorelaxation in human umbilical veins through the activation of K_{ATP}

Sulfatonic®

channels. These findings underscore the context- and vessel-dependent nature of H_2S action in shaping feto-placental hemodynamics.

The role of H_2S in embryo implantation

H_2S facilitates embryo implantation by promoting endometrial receptivity and embryo–epithelial adhesion. In vitro, silencing CBS in JAR cells significantly impairs embryo attachment to Ishikawa cells, indicating the role of CBS-derived H_2S in supporting adhesion via the transsulfuration pathway [160]. In vivo, inhibition of H_2S synthesis reduces implantation site numbers, likely by interfering with CFTR-mediated transepithelial anion transport and altering the uterine microenvironment [161]. These findings suggest that H_2S contributes to the establishment of implantation niches, thereby initiating successful placental development.

H_2S and placental angiogenesis

Placental angiogenesis is primarily regulated by local signaling molecules rather than autonomic innervation. H_2S complements the roles of NO [5] and CO [162] by promoting endothelial proliferation, migration, and tube formation. CBS and CSE are highly expressed in placental endothelial and trophoblast cells, with CBS also found in Hofbauer cells [158, 163–165]. Reduced expression of these enzymes in preeclamptic placentas correlates with impaired angiogenesis, diminished trophoblast invasion, and SAR defects [158, 165]. Existing evidence suggests that H_2S critically modulates placental angiogenesis (Fig. 3).

Mechanistically, H_2S enhances VEGF expression by stabilizing VEGF mRNA and downregulating microRNAs such as miR-200c, miR-20a, and miR-20b, which suppress VEGF synthesis and release [57, 166]. Wang et al. reported that H_2S donors also upregulate PlGF while suppressing antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), thus favoring a proangiogenic environment [158]. Beyond VEGF signaling, H_2S activates the PI3K/AKT1–NOS3 and MAPK3/1 pathways, enhancing endothelial NO production and angiogenic potential [167].

Beyond VEGF signaling, H_2S promotes placental angiogenesis via the AKT1–NOS3 and MAPK3/1 pathways. Exogenous H_2S donors (e.g., NaHS) enhance placental EC proliferation, migration, and tube formation, while trophoblast-derived H_2S further facilitates endothelial migration in a paracrine manner [49, 167–169]. Coculture studies show that HTR-8/SVneo cells drive ovine fetoplacental artery ECs migration via CBS-derived H_2S, whereas BeWo cells exhibit a stronger promigratory effect requiring both CBS and CSE. The coordinated inhibition of CBS (with CHH) and CSE (with BCA) abolishes H_2S synthesis in BeWo cells, highlighting cell type-specific regulation. Primary villous trophoblasts, coexpressing CBS and CTH, display the strongest ability to promote endothelial migration. Mechanistically, H_2S activates phosphorylation of AKT1, MAPK3/1, and NOS3; NO production is specifically dependent on the PI3K–AKT1 axis, as blocked by wortmannin, while MAPK3/1 activation may further enhance endothelial proliferation. These findings support a central role for H_2S in coordinating trophoblast–endothelial crosstalk during placental vascular development.

H_2S and placental vascular dysfunction in pregnancy complications

Defective H_2S signaling has been linked to impaired placental perfusion and vascular maladaptation in disorders such as PE and intrauterine growth restriction (IUGR). H_2S donors (e.g., NaHS) promote vasodilation in placental vessels through mechanisms partially dependent on K_{ATP} channels and NO, indicating synergistic crosstalk between gasotransmitters [64]. In PE placentas with abnormal umbilical artery flow, CSE expression and H_2S production are significantly reduced, which may contribute to increased vascular resistance and trophoblast–endothelial dysfunction [163, 170]. Additionally, microRNA-21 downregulates CSE and its transcription factor SP1, reducing H_2S biosynthesis while promoting SMC proliferation, thereby exacerbating vascular stiffness [171]. Cindrova-Davies et al. reported that loss of CBS function in animal models results in defective decidualization and implantation failure, further emphasizing the importance of H_2S at the maternal–fetal interface [83, 172]. Through its effects on immune modulation, oxidative stress attenuation, and trophoblast invasiveness, H_2S supports both structural and functional adaptation of the uteroplacental vasculature.

H_2S promotes trophoblast invasion by regulating mitochondrial dynamics

The migration and invasion of CTBs are critical biological processes for SAR [173] and normal placental development [173, 174]. Studies suggest that mitochondrial dynamics—particularly the balance between mitochondrial fusion and fission—are pivotal in maintaining CTB motility, with their disruption linked to impaired invasion and vascular remodeling [175, 176]. In the human trophoblast cell line HTR-8/SVneo, inhibition of endogenous CBS impairs CTB invasion and migration, while the exogenous H_2S donor GYY4137 enhances CBS/H_2S mitochondrial translocation, preserves mitochondrial function, and promotes CTB motility [177]. Similar pro-invasive effects of H_2S have been observed in $CBS^{+/-}$ mouse models, where it prevents early pregnancy loss and enhances CTB migration in vitro [24]. Mechanistically, H_2S mediates its effects through the persulfidation

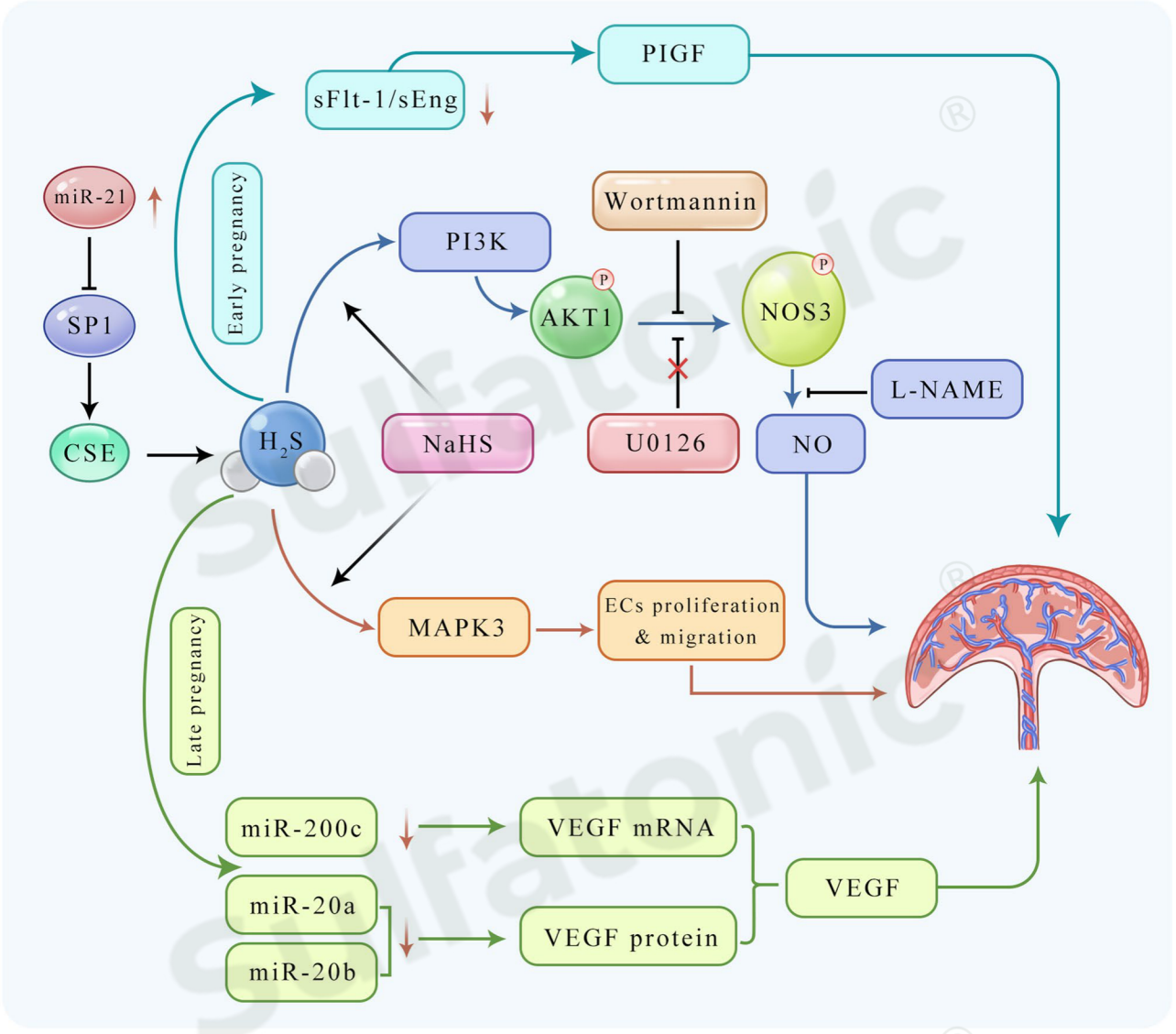


Fig. 3 Multiple Mechanisms of H_2S in Regulating Placental Angiogenesis. H_2S modulates placental vascular function and trophoblast invasion through multiple pathways, facilitating adaptive adjustments in placental blood flow. In early pregnancy, CBS-mediated H_2S production increases, which downregulates sFlt-1 and sEng expression, thereby enhancing PlGF levels and promoting trophoblast invasion, facilitating placental implantation and early development. In late pregnancy, H_2S regulates VEGF release by inhibiting miR-200c targeting VEGF mRNA and suppressing miR-20a and miR-20b targeting VEGF protein. This process enhances VEGF release, promotes placental vascular dilation, and optimizes placental blood flow supply. Overexpression of miR-21 inhibits CSE and SP1 transcription factors, reducing placental H_2S production. Additionally, miR-21 promotes the proliferation of VSMCs while inhibiting their differentiation, thereby affecting placental vascular function. H_2S primarily enhances NOS3 phosphorylation through the AKT1-NOS3 signaling pathway, which promotes NO production, leading to vasodilation and improved blood perfusion. The PI3K-specific inhibitor Wortmannin blocks NOS3 phosphorylation, whereas the MAPK3/1-specific inhibitor U0126 does not affect NOS3 activity. Moreover, H_2S activates the MAPK3/1 signaling pathway, enhancing placental endothelial cell proliferation and migration, further promoting placental angiogenesis. The H_2S donor NaHS significantly enhances these effects. Notes: sFlt-1: Soluble fms-like tyrosine kinase-1; sEng: Soluble endoglin; PlGF: Placental growth factor; VEGF: Vascular Endothelial Growth Factor; PE: Preeclampsia; SP1: Specificity Protein 1; NO: Nitric Oxide; miR-21: miRNA-21; VSMCs: Vascular Smooth Muscle Cells; AKT1: AKT Serine/Threonine Kinase 1; NOS3: Nitric Oxide Synthase 3; MAPK3/1: Mitogen-Activated Protein Kinase 3/1

of mitochondrial Rho GTPase 2 (Miro2) at cysteine residues C185 and C504, which is essential for maintaining mitochondrial morphology and CTB invasion capacity [177]. Mutation of these sites or knockdown of Miro2 leads to mitochondrial fragmentation and impaired trophoblast migration, and notably, GYY4137 fails to rescue mitochondrial dysfunction in Miro2 mutants, confirming the critical role of Miro2 persulfidation in H_2S signaling.

These findings suggest that CTB invasion is modulated by low concentrations of H_2S, with CBS/H_2S maintaining mitochondrial function through Miro2C185/C504 persulfidation, thereby increasing the CTB migration

capacity. Previous research has identified mitochondrial fission regulator 1-like protein (MTFR1L) in HTR-8/SVneo cells as a protein with two distinct H_2S-mediated persulfidation sites [76]. In addition to Miro2, MTFR1L has also been identified as a downstream target of H_2S. MTFR1L is expressed in HTR-8/SVneo cells and plays a key role in mitochondrial structure maintenance [178]. Under CBS/H_2S signaling, MTFR1L undergoes persulfidation at cysteine residues C222 and C230, enhancing mitochondrial integrity and promoting CTB function. Mutation at either site disrupts mitochondrial network formation and reduces CTB invasion capacity, underscoring the functional importance of MTFR1L modification. Importantly, reduced MTFR1L expression and persulfidation levels have been observed in models of great obstetric syndrome models, such as PE and IUGR [178]. Restoration of MTFR1L levels by GYY4137 in hypoxic mouse placentas further confirms the protective role of H_2S in maintaining mitochondrial dynamics and trophoblast invasiveness. Together, these findings underscore the importance of the H_2S-CBS-mitochondria axis in CTB invasion and pregnancy-related disorders (Fig. 4), offering new insights for IUGR and PE intervention strategies.

Chu et al. [179] further supported these findings by demonstrating that the downregulation of CBS and CSE—but not 3-MST—may account for the reduced free H_2S production and diminished cellular H_2S levels observed in pre-eclamptic placentas. Their data also suggest that 3-MST expression in trophoblasts may be developmentally regulated across gestation. This decline in H_2S biosynthesis may exacerbate trophoblast dysfunction by promoting vasoconstriction, oxidative stress, and inflammatory responses—hallmarks of pre-eclampsia. Consistently, Du et al. showed [180] that H_2S supplementation alleviated PE symptoms in vivo by suppressing Toll-like receptor 4 (TLR4)-mediated neuroinflammation in the rostral ventrolateral medulla.

H_2S regulates UA vasodilation and perfusion to support placental development

Adequate uterine perfusion is a prerequisite for proper placental development and fetal growth. During pregnancy, the maternal cardiovascular system undergoes significant adaptive changes, including increased blood volume and cardiac output, systemic vasodilation, and decreased vascular resistance, whereas blood pressure remains stable or only slightly decreases [154, 155, 181]. These physiological changes prioritize blood flow to the uterus, significantly increasing perfusion at the maternal–fetal interface to meet the metabolic demands of rapid placental and fetal growth. In nonpregnant sheep, reproductive organs receive only 1%–2% of cardiac output, whereas in late pregnancy, this proportion increases to 15%–20%, with over 95% of the flow directed to the uteroplacental vasculature, increasing UtBF from 10 mL/min in nonpregnant sheep to 500–800 mL/min in pregnancy [154]. This substantial increase in UtBF is crucial for maternal–fetal gas exchange (O_2/CO_2) and placental–fetal growth, making UtBF a direct determinant of pregnancy outcomes. In recent years, H_2S has emerged as a novel vasodilator, gaining increasing attention for its role in regulating UtBF during pregnancy [182–184]. Studies indicate that H_2S influences UAs by modulating CSE/CBS-mediated H_2S production, promoting UA relaxation, regulating potassium ion channels (particularly BK_{Ca} channels) through S-sulfhydration, and interacting with NO and CO to maintain vascular homeostasis. The following sections will explore the molecular mechanisms underlying H_2S regulation of UA blood flow and its interactions with NO and CO (Fig. 5).

Molecular mechanisms of H_2S-mediated UA relaxation

H_2S acts as a potent vasodilator and proangiogenic factor, primarily synthesized in UAs via CSE and, under pregnancy or estrogen stimulation, via upregulated CBS expression [58, 70, 71, 84, 184]. In pregnant human UA endothelial cells (P-hUAECs), VEGF selectively enhances CBS-mediated H_2S production, independent of CSE, a process further amplified during pregnancy [58]. This indicates a shift toward CBS dominance in pregnancy-specific vascular adaptation. Distinct from NO and CO, H_2S induces endothelium-independent relaxation of vascular smooth muscle cells (VSMCs) by activating K_{ATP} channels, while also enhancing NO signaling through endothelial nitric oxide synthase (eNOS) activation [64, 185]. This dual mechanism allows H_2S to compensate for impaired endothelial function and maintain UA tone during gestation.

Functional assays support this role of H_2S donors, such as GYY4137 and NaHS, induce dose-dependent relaxation in UAs of both rodents and humans, with stronger responses observed during pregnancy [54, 71, 186]. Notably, this vasodilatory effect is vascular bed specific, with UAs demonstrating higher sensitivity to H_2S than in mesenteric arteries [71, 186], suggesting a specialized regulatory role of H_2S in uteroplacental hemodynamics.

S-sulfhydration and potassium ion channels in H_2S-mediated UA relaxation

S-sulfhydration, a key posttranslational modification by H_2S, enhances protein reactivity by converting Cys-SH groups to -SSH [187, 188]. Bai et al. reported that the levels of S-sulfhydrated proteins in UAs from pregnant women were significantly greater than those in nonpregnant sheep women [51]. Additionally, Yadav et al. demonstrated that dithiothreitol, a thiol-reducing agent, inhibits NaHS-induced UA relaxation in rats, further supporting

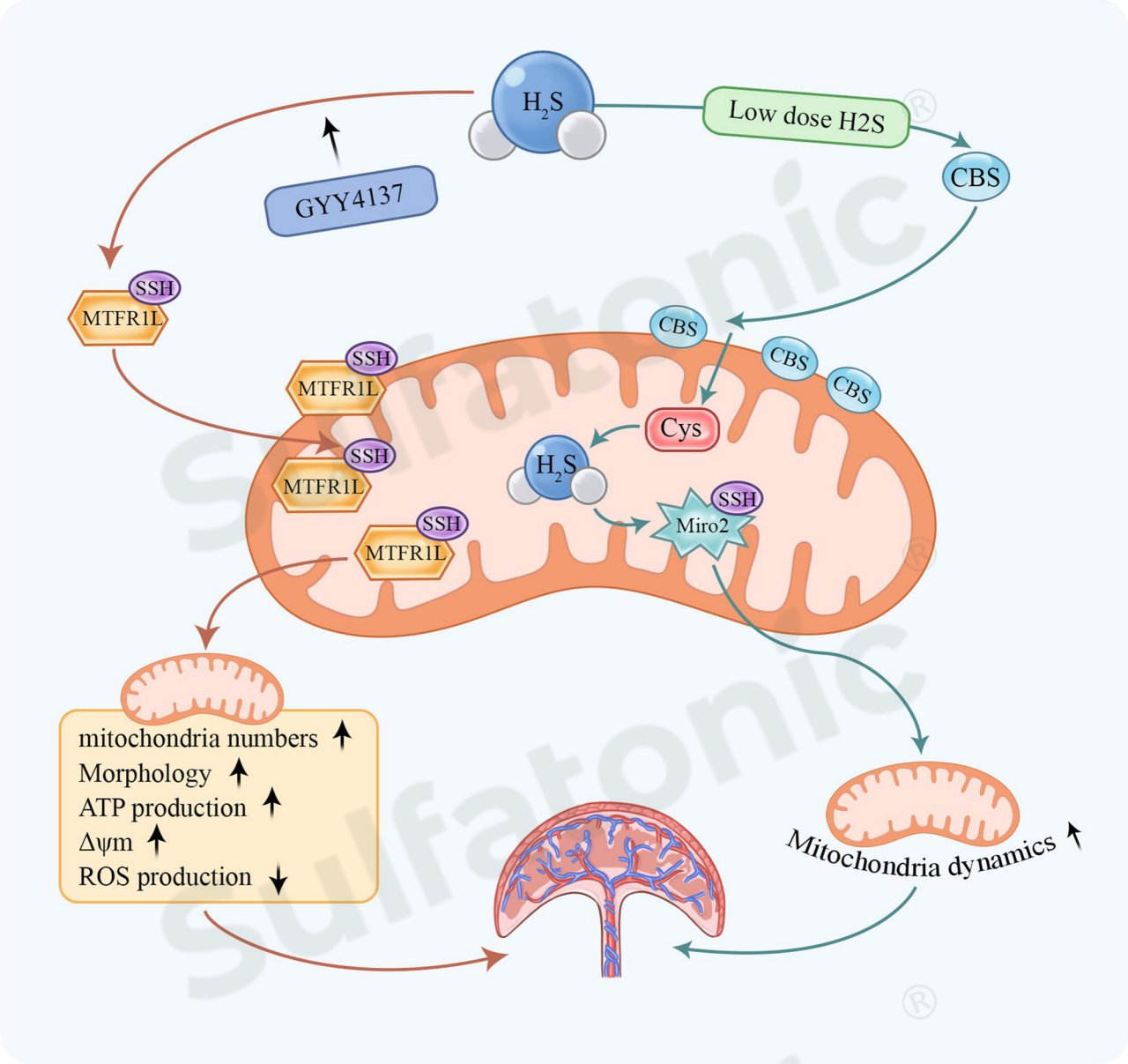


Fig. 4 H_2S Promotes Trophoblast Invasion by Regulating Mitochondrial Dynamics. In normal pregnancy, H_2S promotes the persulfidation of MTFR1L, maintaining its stable expression and ensuring mitochondrial quantity, morphology, and function, including adequate ATP production, low ROS levels, and a high Δψm. These factors are crucial for trophoblast invasion and migration. The H_2S donor GYY4137 further enhances this regulatory effect, supporting normal placental function. Low-dose H_2S can stimulate CBS translocation to mitochondria, inhibit its degradation, and promote CBS aggregation on mitochondria, enabling Cys to be catalyzed into H_2S within mitochondria. Mitochondrial CBS/H_2S subsequently sulfhydrates Miro2-C185, promoting mitochondrial dynamics, thereby enhancing trophoblast invasion and migration. Notes: MTFR1L: Mitochondrial Fission Regulator 1-Like; ROS: Reactive Oxygen Species; Δψm: Mitochondrial membrane potential; Cys: L-cysteine

the essential role of S-sulfhydration in H_2S-mediated vasodilation [186]. Notably, disrupted S-sulfhydration is associated with pregnancy complications such as PE [52, 158, 189–191].

Among the downstream targets, K_{ATP} channels are critical mediators of H_2S-induced vasorelaxation. Although systemic arteries often rely on K_{ATP} channels activated via S-sulfhydration of the Kir6.1 pore subunit (Cys43) and the ATP-binding cassette protein SUR2B subunit (Cys24, Cys2455) [52, 192], their role in UAs is limited [54]. Nevertheless, Bai et al. detected significantly higher S-sulfhydration levels of Kir6.1 and SUR2B in UAs from pregnant women compared to nonpregnant women [51], suggesting that S-sulfhydration may contribute to K_{ATP} channel regulation during pregnancy, although its exact role in H_2S-mediated UA relaxation requires further

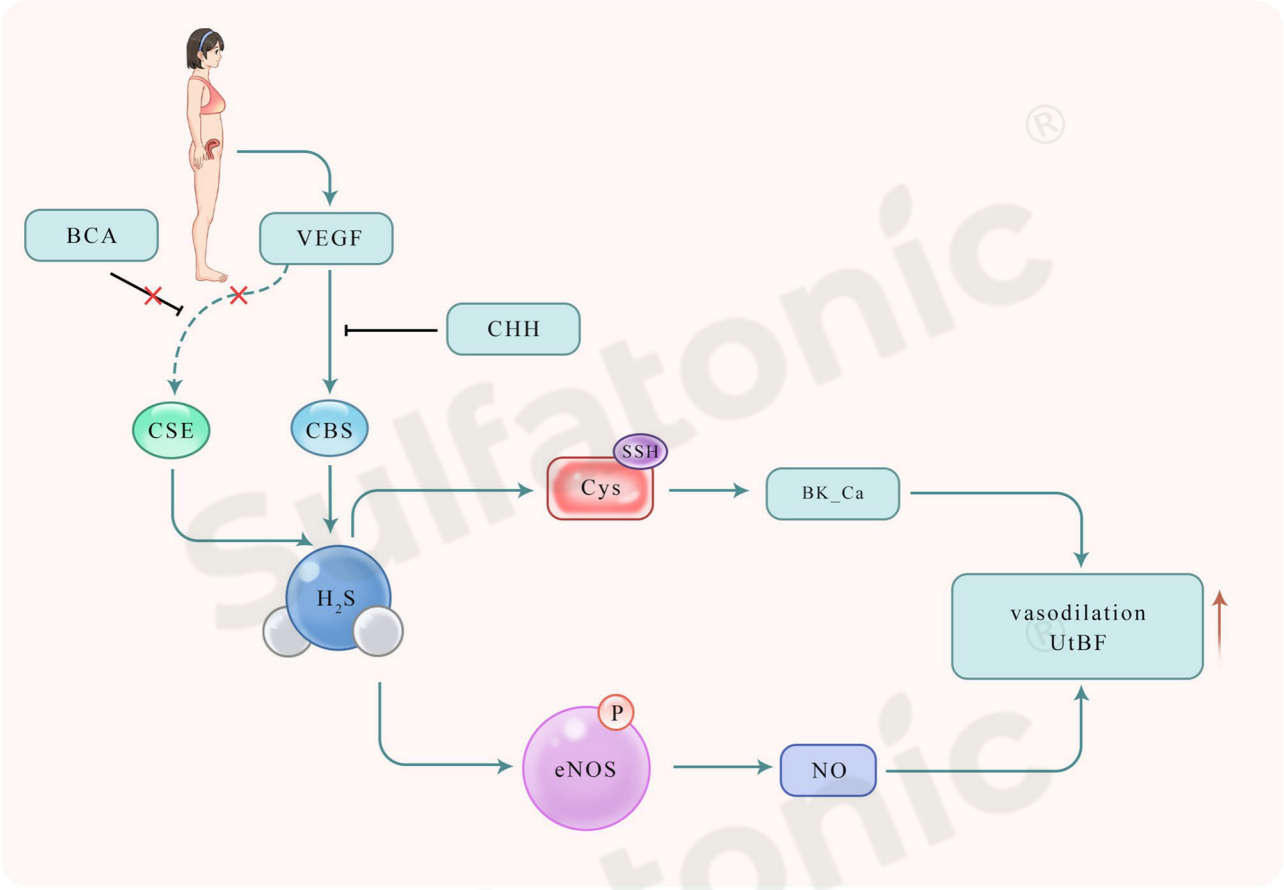


Fig. 5 H_2S-Mediated UA Vasodilation. Pregnancy enhances VEGF-induced signaling, selectively upregulating CBS without affecting cystathionine γ-lyase CSE. This promotes CBS-mediated H_2S production, which in turn enhances S-sulfhydration of L-cysteine residues, leading to BK_Ca channel activation and subsequent vascular relaxation, thereby increasing uterine arterial blood flow. Additionally, H_2S facilitates eNOS phosphorylation, augmenting NO production, which further amplifies NO-dependent vasodilation, contributing to improved uteroplacental circulation. Notably, CBS inhibition CHH completely blocks VEGF-induced H_2S production, whereas CSE inhibition BCA has no significant effect, confirming CBS as the primary source of H_2S in this process. Notes: CHH: O-(carboxymethyl)hydroxylamine hemihydrochloride; BCA: b-Cyano-L-alanine; eNOS: Endothelial Nitric Oxide Synthase

investigation. Bai et al. also identified the BK_{Ca} channel α-subunit as a novel S-sulfhydration target, with Cys710 undergoing S-sulfhydration [51], consistent with its essential role in H_2S-induced relaxation [54, 186]. Inhibitors of BK_{Ca}—but not K_{ATP} or voltage-gated K^+ channels—abolish H_2S-induced vasodilation in both rats and humans [54, 186], and patch-clamp data confirm selective BK_{Ca} activation by H_2S [54, 186].

In addition to potassium channels, L-type Ca^{2+} channels are also abundantly expressed in uteroplacental smooth muscle and play a central role in regulating vascular tone, particularly under hypoxic conditions [193, 194]. Tropea et al. reported [195] that L-type Ca^{2+} channels and extracellular signal regulated kinase (ERK1/2) signaling contribute to G1-mediated vasorelaxation in UAs. Moreover, Corcoran et al. [196] demonstrated that pre-incubation with the L-type Ca^{2+} channel agonist Bay K8644 enhances estrogen-induced vasodilation in placental arteries. While the direct interaction between H_2S and L-type Ca^{2+} channels in uteroplacental vessels has not been fully elucidated, Munaron et al. showed [197] that H_2S interferes with calcium homeostasis in neurons, cardiomyocytes, and ECs through modulation of Ca^{2+} channels, suggesting a potential cross-talk mechanism worth further investigation.

Collectively, these findings highlight a pregnancy-specific mechanism in which H_2S promotes uterine vasodilation predominantly through S-sulfhydration and BK_{Ca} channel activation, underscoring its potential as a therapeutic target in pregnancy-related vascular disorders.

Interactions of H_2S, NO, and CO in UA regulation

The interactions among NO, CO, and H_2S add complexity to gaseous signaling in the vascular system, particularly in the uterine vasculature. Studies indicate that these three gaseous molecules are synthesized in UA ECs and/or VSMCs, where they independently or synergistically regulate vascular tone and homeostasis [64,

Sulfatonic®

198]. During pregnancy, their interplay contributes to the dynamic vascular adaptations required for adequate placental perfusion. H_2S and NO often exhibit cooperative effects on vasodilation and angiogenesis. H_2S can enhance NO signaling by upregulating eNOS phosphorylation and NO production [49, 168], and its vasodilatory effect is partially inhibited by NOS blockade, suggesting upstream modulation of the NO pathway [64]. However, their interaction is not always synergistic. Some studies have shown that NaHS treatment attenuates the vasodilation induced by NO donors (SNP, SIN-1, and SNAP) [199], suggesting that H_2S and NO may form products lacking vasodilatory properties. For example, NO/H_2S interactions can generate $SSNO^-$, a molecule with prolonged activity [200]. In rat uterine studies, GSNO (an NO donor) had a weaker relaxant effect on uterine smooth muscle contraction than H_2S did, whereas the combination of H_2S and GSNO reduced vasodilation, even at a 1:10 ratio [201].

The interaction between H_2S and CO is less understood. H_2S may enhance CO production via heme oxygenase-1 (HO-1) upregulation under hypoxic conditions, indicating possible synergy in pulmonary vascular regulation [202]. Yet, suggesting that H_2S and CO may act synergistically in pulmonary arterial SMCs to regulate vascular tone. In contrast, in vitro studies on aortic SMCs indicate that H_2S and CO may have antagonistic effects. Inhibition of HO-1 (a CO-producing enzyme) reduces CSE expression and H_2S production, whereas CSE inhibition increases HO-1 expression and CO production. However, exogenous NaHS (100 μM) decreases HO-1 expression [203]. Moreover, CO can either stimulate or inhibit sGC depending on NO levels, futher complicating the gasotransmitter crosstalk [204]. The complex interplay among NO, CO, and H_2S in the vascular system, particularly in the uterine circulation, requires further investigation to determine their precise physiological significance in pregnancy-related vascular adaptation and placental perfusion regulation.

The role of H_2S in maternal–fetal immune tolerance and oxidative stress regulation

The establishment of maternal–fetal immune tolerance is essential for a successful pregnancy and relies on the coordination between trophoblasts, decidual stromal cells, and maternal immune cells [205, 206]. A shift from a T-helper 1 (Th1)- to T-helper 2 (Th2) -dominant immune response is required to promote fetal tolerance [207]. H_2S, H_2S, mainly synthesized by CBS at the maternal–fetal interface, regulates immune homeostasis by modulating inflammatory signaling and immune cell function. H_2S inhibits the TLR4/nuclear factor-kappa B (NF-κB) pathway, reducing proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [208–214]. Wang et al. [24] revealed that the expression of NF-κB-related genes in HTR8/SVneo cells is affected by changes in CBS levels. Additionally, H_2S promotes regulatory T cell (Treg) differentiation and maintains uNK cell populations, both essential for decidualization and SAR [172, 215].

Beyond immune regulation, H_2S also protects against oxidative stress and ischemia-reperfusion injury by activating pro-survival pathways, such as AKT, PKC, and ERK1/2 pathway [216, 217], enhancing eNOS-mediated NO production [217] and promoting antiapoptotic genes expression via NF-κB [218]. H_2S exerts antioxidant effects by directly scavenging reactive oxygen species and activating the nuclear factor erythroid 2-related factor 2 pathway, which upregulates antioxidant enzymes such as HO-1 and glutathione peroxidase [219–221]. It also supports endoplasmic reticulum stress adaptation by enhancing GSH synthesis via the transsulfuration pathway [222]. In the placenta, hypoxia/reoxygenation (H/R) stress impairs trophoblast viability, migration and invasion [223]. H_2S donors have shown protective effects against H/R injury in the heart [224], kidneys [225], and neurons [226], suggesting a potential role for H_2S in restoring trophoblast function and mitigating and pregnancy-related complications.

Regulation of H_2S synthesis and function by Estrogen

H_2S plays a crucial role in regulating UtBF, promoting SAR, and maintaining placental oxidative homeostasis during pregnancy. Its biosynthesis and signaling are modulated by various factors, among which estrogen is a key hormonal regulator. Studies have shown that H_2S production in UA endothelium and smooth muscle is positively correlated with endogenous estrogen levels [71]. Moreover, CBS mRNA/protein expression and H_2S production in the endometrium increase significantly during the proliferative phase and pregnancy, correlating positively with estrogen-driven angiogenesis. These findings underscore the importance of estrogen in orchestrating H_2S-mediated vascular and placental adaptations, offering insights into pregnancy physiology and potential targets for related complications.

Types of estrogens and their dynamic changes during pregnancy

Estrogens are steroid hormones produced primarily by the ovaries, placenta, with dynamic shifts during pregnancy. In early pregnancy, the corpus luteum remains the primary source of estrogen, but by weeks 9–10, the placenta becomes the primary source via STB, relying on androgen precursors from maternal and fetal adrenal glands [227, 228]. Due to the absence of 17α-hydroxylase-17,20-lyase in the placenta, estrogens are synthesized through peripheral precursor aromatization [229, 230]. :

estrone (E1), estradiol (E2), estriol (E3) and estetrol (E4). E1 is mainly derived from ovaries and adipose tissue, biologically weak. E2 is the most biologically active estrogen, initially from the ovaries, later predominantly placental [231, 232]. E3 is predominantly secreted by the placenta, with over 90% released into the maternal circulation by STBs in humans due to their haemochorial [233, 234]. E4 is synthesized mainly by the fetal liver, unique to humans and higher primates [235, 236].

During pregnancy, estrogen levels exhibit significant dynamic changes, particularly E2, which may reach concentrations up to 1,000 times than in the nonpregnant state [230, 237, 238]. These elevations accompany systemic vascular changes, including decreased resistance, increased cardiac output and blood volume, and a significant redistribution of blood flow to the uterus and placenta (15–20% of cardiac output) [3, 154, 239]. This estrogen-driven hemodynamic remodeling provides a favorable environment for H_2S biosynthesis and vascular actions.

The complex role of Estrogen in the hemodynamic regulation of UtBF

A critical function of estrogen during pregnancy is to increase UtBF and support placental perfusion [240]. UtBF exhibits a cyclical increase [3, 154, 239], peaking in mid- and late pregnancy, coinciding with placental formation and rapid fetal growth [3]. Moreover, circulating and/or local estrogen levels increase synchronously as UtBF peaks [241–243]. As early as 1932, Markee reported that estrogen induced hyperemia in uterine tissue transplanted into the eyes of monkeys [244], and later, Rosenfeld and Magness confirmed estrogen's profound impact on reproductive tract vasculature using ovariectomized (OVX) nonpregnant and pregnant ewe models [245, 246]. Estrogen acts on UA endothelial and SMCs via estrogen receptors (ERs) to regulate vascular tone [247–250]. This approach allows E_2 to influence vascular function via genomic and nongenomic mechanisms. In genomic mechanisms (ERα/ERβ), E_2 activates NOS through ERs, promoting NO synthesis [251, 252] and inducing vasodilation [196, 253, 254]. Nongenomic mechanisms effects via G protein-coupled estrogen receptor (GPER) may enhance H_2S production in UAECs and UASMCs [71, 184], contributing to smooth muscle relaxation through BK_{Ca} channels activation, mimicking NO effects.

Although NO is a major mediator of estrogen-induced vasodilation, studies show that NO inhibition accounts for only part of the effect (≈79% of UtBF increase; ≈26% of basal UA dilation), implying the existence of additional mediators, notably H_2S [47, 251]. Estrogen also regulates UtBF via NO-independent pathways, including direct actions on UA SMCs to reduce myogenic tone and enhance BK_{Ca}-mediated relaxation [255–258], involving signaling pathways such as ERK1/2, PKC signaling [259], and cyclic guanosine monophosphate (cGMP) [251, 259–261]. Other vasodilators (prostaglandin I2 [262], CO [48], and EDHR [263]) may act synergistically with H_2S and NO.

Beyond vasodilation, estrogen exerts trophic effects at the maternal-fetal interface [264]. E_2 acts on STBs, CTBs, and invasive EVTs via ERs, promoting EVT invasion, regulating trophoblast survival, differentiation, and proliferation, and facilitating SAR to enhance placental perfusion [265–267]. Estrogen also maintains placental microenvironment homeostasis by modulating ECM remodeling and migration [268]. Overall, estrogen increases UtBF through multiple pathways, including both NO-dependent and NO-independent mechanisms. The identification of H_2S as a novel regulatory mediator downstream of estrogen highlights its emerging role in maintaining uteroplacental hemodynamics and points to new therapeutic targets for pregnancy-related vascular disorders.

Mechanisms of estrogen-mediated regulation of H_2S production

H_2S is synthesized primarily by CBS, CSE, and 3-MST. Estrogen regulates the expression and activity of these enzymes through both genomic and nongenomic mechanisms, thereby increasing H_2S production (Fig. 6).

ER receptor-mediated transcriptional regulation of CBS

Estrogen receptors ERα and ERβ display tissue-specific expression patterns. ERα is predominantly expressed in the pituitary, kidneys, and reproductive tissues, while ERβ is more widely distributed, particularly in reproductive organs and the brain [269]. In the utetus and ovaries, both ERα and ERβ are highly expressed, reflecting the female reproductive system as a primary target of estrogen signaling [270, 271]. UAs, comprising ECs and SMCs, express ERα, ERβ, and GPER [249, 272, 273].

Estrogen selectively upregulates CBS, not CSE, to increase H_2S production. In OVX nonpregnant ewes, estrogen replacement increases CBS mRNA/protein expression and H_2S levelswithout affecting CSE [184]. During the follicular phase, proliferative phase, and pregnancy, increased endogenous estrogen levels parallels elevated CBS expression and H_2S synthesis, whereas CSE and 3-MST remain unchanged [71]. In vitro studies in sheep and human UAECs and UASMCs confirme that E_2 induces CBS mRNA/protein expression [78, 274, 275]. Although CSE is induced by E_2 in sheep UAECs, this effect is absent in human UAECs [275]. Regardless, both exogenous and endogenous estrogen consistently promote H_2S production via CBS. In human primary UAECs, E_2 upregulates CBS and H_2S more robustly in cells derived from pregnant than nonpregnant individuals [275]. CBS is a classical estrogen-responsive gene,

Sulfatonic®

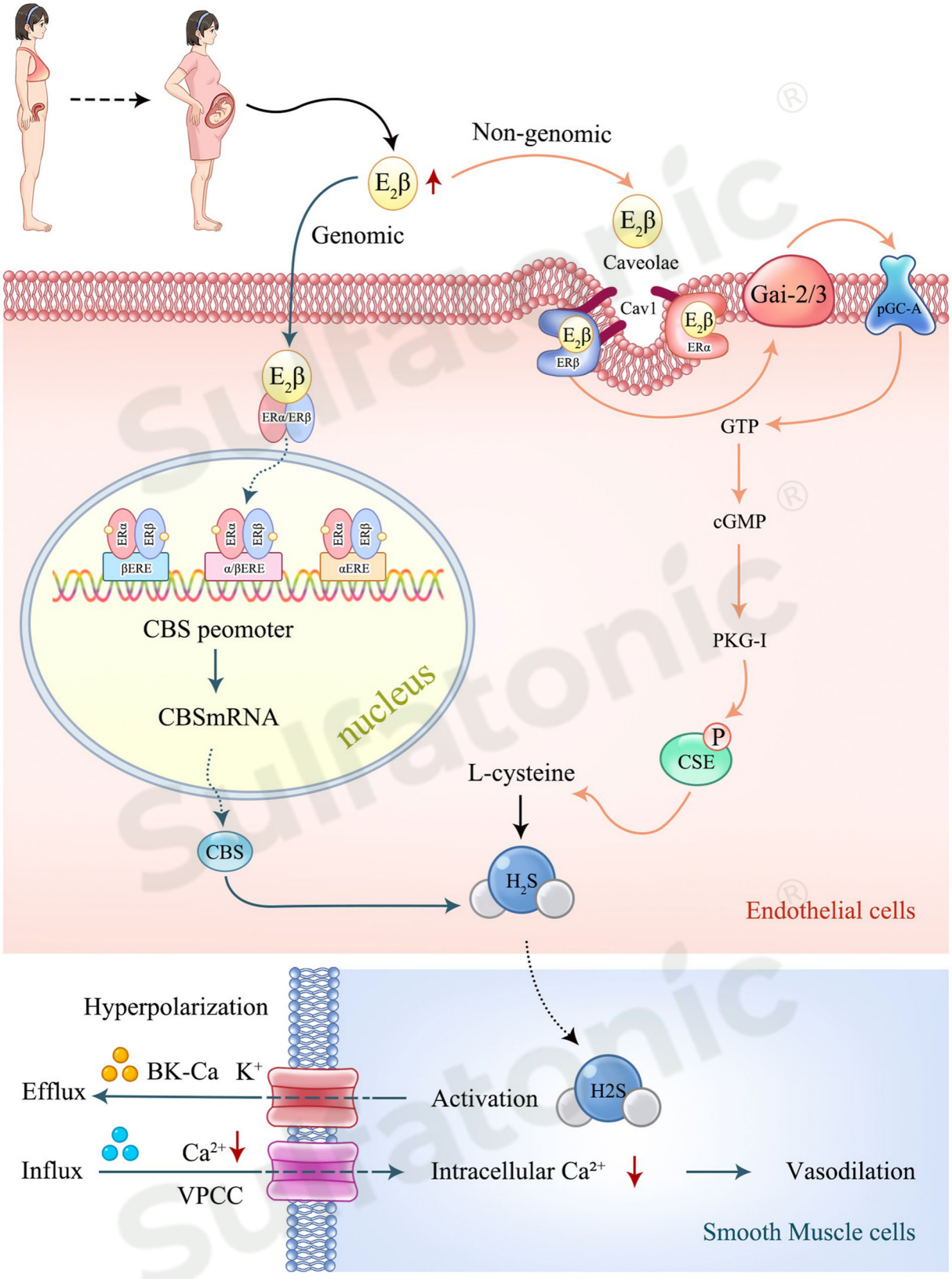


Fig. 6 (See legend on next page.)

(See figure on previous page.)

Fig. 6 Estrogen-Regulated H_2S Pathways in Uterine Vasodilation. H_2S mediates estrogen ($E_2\beta$)-induced uterine vasodilation through genomic and non-genomic mechanisms. Genomic Pathway: $E_2\beta$ crosses the cell membrane and binds to ERα and ERβ, which function as nuclear TFs. Upon binding to EREs, these receptors promote CBS gene transcription. The human CBS promoter contains multiple ERE sites, including αERE (ERα binding site), three βEREs (ERβ binding sites), a full α/βERE, and a half α/βERE (½α/βERE). Among these, α/βERE2 and ½α/βERE1 are crucial for basal CBS expression and E_2-induced CBS promoter activation. ERα and ERβ can form homodimers (ERα/ERα or ERβ/ERβ) or heterodimers (ERα/ERβ), regulating H_2S production.Non-Genomic Pathway: $E_2\beta$ binding to membrane-associated ERα and ERβ directly activates Gαi-2/3, which subsequently stimulates pGC-A, catalyzing GTP conversion to cGMP. cGMP then activates cGMP-dependent PKG-I, which phosphorylates CSE, enhancing H_2S production. The generated H_2S diffuses into SMCs, promoting vasodilation via K-ATP or BK-Ca channels, thereby increasing uterine arterial blood flow. Notes: EC: endothelial cell; SMC: smooth muscle cell; TFs: transcription factors; EREs: estrogen response elements; pGC-A: particulate guanylate cyclase A; PKG-I: protein kinase I

the transcription of which is regulated by estrogen genomic signaling. The ER antagonist ICI 182, 780 blocks E_2-induced CBS promoter activity, confirming transcriptional regulation via ERs [78, 274].

ERα and ERβ act as nuclear transcription factors (TFs) binding to estrogen response elements (EREs) within the CBS promoter [248], which includes one αERE (binding ERα), three βEREs (binding ERβ), one full α/βERE, and one half α/βERE (½α/βERE). of these, α/βERE2 and ½α/βERE1 are essential for both basal CBS expression and E_2-stimulated CBS promoter activation [274]. UAECs and UASMCs express both ERα and ERβ, which can form homodimers (ERα/ERα or ERβ/ERβ) or heterodimers (ERα/ERβ) [78]. This effect is blocked by ERα antagonist (MPP) or ERβ antagonist (PHTPP) [275], while ERα-selective agonist (PPT) and ERβ-selective agonist (DPN) mimic E_2 action, suggesting equal regulatory potential [275]. while the CSE promoter also contains EREs, it is not transcriptionally responsive to estrogen, reinforcing CBS's unique sensitivity to estrogenic regulation in the uterine vasculature. Additionally, the CBS promoter contains Sp1 and YY1 binding sites, and VEGF enhances CBS transcription through these TFs, promoting H_2S production [276]. ERα and ERβ can also interact with Sp1 [277], suggesting that future research should explore ER-associated TFs involved in estrogen-induced CBS transcription and H_2S production.

Estrogen promotes H_2S production via nongenomic signaling

Beyond transcriptional control, estrogen rapidly promote H_2S production through nongenomic signaling pathways. Estrogen binding to membrane ERs (primarily ERα/ERβ) activates Gαi-2/3 proteins, which in turn stimulate particulate guanylate cyclase A (pGC-A), converting GTP to cGMP. cGMP activates protein kinase G (PKG-I), which phosphorylates CSE, boosting enzymatic activity and H_2S synthesis [278]. The generated H_2S diffuses into SMCs, promoting vasodilation. This pathway is functionally critical, as silencing of CSE or pGC-A impairs E_2-induced vasodilation in mouse aortic experiments [278]. PKG directly phosphorylates CBS (at Ser227), further increasing its catalytic function [279]. While GPER contributes to uterine vasoregulation, its direct role in nongenomic H_2S production remains uncertain. GPER may indirectly influence H_2S via PI3K/Akt-eNOS-NO signaling cascades [280], warranting further investigation. Overall, E_2 enhances H_2S production by rapidly phosphorylating CSE through the ER-Gαi-2/3–cGMP–PKG-I pathway, whereas the direct involvement of GPER remains inconclusive. However, further studies are needed to elucidate whether GPER influences H_2S production through alternative signaling pathways.

The potential role of H_2S and its donors in pregnancy-related disorders

As an essential gasotransmitter, H_2S freely permeates cell membranes without requiring specific transport proteins, thereby rapidly activating biological signaling [281, 282]. The rational design and delivery of H_2S donors are crucial for mimicking endogenous H_2S function and optimizing pharmacological effects. To date, a wide range of H_2S donors have been developed, including inorganic salts [283–285], organic compounds [286–288], slow-releasing systems [289, 290], fluorescently labeled probes [291], and polymer-based smart delivery platforms [292, 293]. These formulations aim to optimize H_2S release kinetics, enhance tissue targeting, and improve biocompatibility [294]. Additionally, several emerging H_2S donors, such as thiol-activated donors, metal complex-based donors, sulfur-containing amino acid derivatives, and persulfide-based donors, are being explored [295]. Despite promising in vitro and in vivo data, most H_2S donors still lack comprehensive pharmacokinetic and toxicological profiling, and their clinical translation remains limited.

Research and applications of H_2S donors in pregnancy complications

H_2S has been increasingly recognized as a critical regulator of pregnancy physiology, exerting vasodilatory, anti-inflammatory responses, antioxidation, and cytoprotection. However, the direct clinical application of gaseous H_2S is constrained by its volatility, toxicity, and challenges in dose control. To overcome these limitations, various H_2S-releasing compounds have been developed to enable controlled, sustained delivery of H_2S. These donors offer a promising strategy for restoring H_2S homeostasis in pregnancy-related disorders, particularly PE, FGR, and placental dysfunction. Table 1 summarizes the major types of H_2S donors and their potential applications in obstetric complications.

PE

PE is a major hypertensive disorder of pregnancy, affecting 4–7% of pregnancies worldwide and contributing to significant maternal and perinatal morbidity and mortality worldwide [296]. Despite extensive research, effective preventive and treatment remain limited. Placental ischemia and maternal endothelial dysfunction are key pathological features of PE [297, 298].

Recent studies have demonstrated that placental H_2S synthesis is impaired in PE, characterized by reduced expression of CBS and CSE, leading to decreased H_2S production and lower maternal plasma H_2S levels [158, 163, 164, 177]. This deficiency is associated with a proantiangiogenic environment and endothelial dysfunction in PE [49, 299]. Feng et al. [177] reported that CBS-derived H_2S maintains mitochondrial function via Miro2C185/C504 persulfidation, which is essential for CTB invasion, migration, and SAR. Wang et al. reported that the inhibition of CSE with DL-propargylglycine reduces placental PlGF expression and suppresses trophoblast invasion, whereas in human umbilical vein ECs, adenovirus-mediated CSE overexpression inhibits the release of sFlt-1 and sEng, suggesting that CSE/H_2S dysregulation may contribute to abnormal placental angiogenesis [158]. Additionally, Bai et al. reported that circulating sFlt-1 levels are significantly elevated in PE mice and that sFlt-1 suppresses VEGF-induced CBS expression, reducing H_2S synthesis [276].

Given the central role of H_2S deficiency in PE pathogenesis, exogenous H_2S supplementation has emerged as a potential therapeutic strategy. Wang et al. [158] reported that in CSE-inhibited PE mouse models, the slow-releasing H_2S donor GYY4137 reduced circulating sFlt-1/sEng levels and reversed PE-like symptoms. Similarly, Yadav et al. [300] showed that in sFlt-1-overexpressing rats, GYY4137 lowered blood pressure, improved UA blood flow, and upregulated eNOS and NO levels, partly by inhibiting adrenergic vasoconstriction. Other donors, such as MZe786 (a novel H_2S-releasing aspirin derivative), ameliorated hypertension and kidney injury in PE mice under high sFlt-1 conditions while enhancing placental antioxidant capacity [301]. Additionally, Du et al. [180] has also shown efficacy in reducing neuroinflammation via suppression of microglial activation in the rostral ventrolateral medulla, potentially regulating sympathetic overactivity in PE.

In vitro and ex vivo studies further support these findings. NaHS induced dose-dependent vasodilation in human placental villous vessels, mediated primarily via K_{ATP} channels [163]. In HTR-8/SVneo trophoblast cells under oxidative stress, NaHS restored mitochondrial function, inhibited apoptosis, and enhanced invasion by modulating Drp1-mediated fission and the B-cell lymphoma-2/Bax-caspase-3 axis [302]. GYY4137 preserved mitochondrial integrity through CBS-mediated persulfidation of Miro2 and MTFR1L, promoting trophoblast motility and SAR in hypoxia-induced models [177, 178].

Moreover, H_2S donors may regulate necroptosis and cytoskeletal dynamics in trophoblasts. Zhang et al. [303] reported that caspase-8/3 expression was downregulated in PE placental tissue, whereas the necroptosis-related proteins receptor-interacting serine/threonine-kinase-1and receptor-interacting serine/threonine-kinase-3 were significantly upregulated. Further studies confirmed that NaHS reduced ceramide-induced trophoblast necroptosis by regulating the p38 MAPK signaling pathway, thus exerting protective effects. To investigate trophoblast migration, Gupta et al. [18] found that in PE placentas, the expression levels of H_2S-producing enzymes (CSE and CBS) were reduced, whereas the Rho family of small GTPases (Rac1 and RhoA) was downregulated. In addition, H_2S may restore the balance of MMPs and their inhibitors disrupted in PE, partly through miR-30b/CSE signaling [304].

Despite these promising results, several challenges remain. Most current studies rely on HTR-8/SVneo cell lines and animal models that may not fully reflect the complexity of human PE. The pharmacokinetics, safety profile, and optimal dosing of H_2S donors during pregnancy also require further investigation. Future work should focus on developing stable, targeted, and biocompatible H_2S-releasing platforms, along with rigorous preclinical and clinical evaluations to explore their translational potential in PE therapy.

Gestational diabetes mellitus (GDM)

The role of H_2S in metabolic regulation has gained increasing attention. Endogenously produced by pancreatic β-cells, liver, adipose tissue, skeletal muscle, and the hypothalamus, H_2S participates in maintaining glucose homeostasis by regulating both local and systemic glucose metabolism [305]. It can inhibit insulin secretion and modulate β-cell apoptosis, with its effects depending on the metabolic microenvironment [306–310]. Clinical studies have shown decreased plasma H_2S levels in diabetic patients, suggesting its involvement in maintaining insulin sensitivity and β-cell function [311–313]. For instance, Okamoto et al. [314] found that CSE-derived H_2S protects β-cells against glucotoxicity by regulating TBP-2 (Txnip), while in CSE-deficient mice on a high-fat diet (HFD), H_2S donor NaHS reduced β-cell DNA fragmentation and TBP-2 expression. Similarly, reduced plasma H_2S levels and CSE expression were associated with insulin resistance (IR) severity in HFD-fed rats [315]. Beyond direct pancreatic effects, H_2S also modulates the gut-insulin axis. Pichette et al. [316] reported that NaHS and GYY4137 stimulated glucagon-like peptide-1 (GLP-1) secretion in mouse L-cells (GLUTag cell line) via the

Table 1 Effects and mechanisms of H_2S donors in pregnancy-related disorders

Disease type, H_2S donor, Chemical type Research model	Mechanism of action	Key effects & findings	Country	Reference
PE				
NaHS				
Inorganic salt (fast-releasing donor)				
Human placental tissue	Activates K_{ATP} channels	Dose-dependent vasodilation of placental villous stromal vessels, reducing perfusion pressure and vascular resistance	UK	[163]
Rat PE model	Inhibits microglia-mediated inflammation in RVLM	Alleviates PE and LPS-induced neuroinflammation and sympathetic overactivation	China	[180]
HUVECs	Reduces sFlt-1 and sEng levels	Reverses anti-angiogenic effects in PE, restores tubular formation capacity of HUVECs	USA	[158]
HTR-8/SVneo	Upregulates Bcl-2 and reduces PRAP, stabilizing mitochondrial membrane potential	Inhibits apoptosis, improving trophoblast survival	China	[302]
	Activates Rho GTPase-mediated cytoskeletal remodeling	Restores trophoblast migration after hypoxia/reoxygenation injury in PE	India	[18]
	Modulates the MMP/TIMP axis	Restores MMP/TIMP balance, enhancing trophoblast invasion, partially reversing invasion impairment after H/R injury	India	[304]
JEG-3	Inhibits p38MAPK activation, reduces RIPA1, RIPA3, and pro-inflammatory cytokine expression	Protects against ceramide-induced necroptosis in trophoblasts	China	[303]
GYY4137				
Organic slow-releasing donor				
Rat PE model	Upregulates eNOS protein expression	Significant antihypertensive effects, restores UA blood flow, reduces RI and PI	USA	[300]
Mouse PE model	Reduces sFlt-1 and sEng levels	Enhances vascular function, improves placental perfusion, and optimizes fetal growth outcomes	USA	[158]
Chronic intermittent hypoxia mouse model	Sulfur-modifies MTFR1L (C222/C230 sites)	Maintains mitochondrial morphology and function, enhances trophoblast migration and invasion	China	[178]
HTR-8/SVneo	Sulfhydration of Miro2C185/C504 maintains mitochondrial function	Regulates mitochondrial function, enhances trophoblast migration and invasion, promotes spiral artery remodeling	China	[177]
MZe786				
H_2S-releasing aspirin				
Mouse PE model	Promotes antioxidant gene expression	Enhances placental antioxidant capacity, alleviates PE-related oxidative stress and vascular dysfunction, lowers hypertension risk, and reduces renal damage	UK	[301]
GDM				
NaHS				
Inorganic salt (fast-releasing donor)				
HTR-8/SVneo	Inhibits NLRP3 inflammasome activation	Suppresses NLRP3 inflammasome activation in human placental cells, reducing insulin resistance	China	[329]
PTB				
NaHS				
Inorganic salt (fast-releasing donor)				
Human myometrial tissue	Mediates K_{ATP} channels	Inhibits the amplitude and frequency of spontaneous contractions; selectively reduces oxytocin-induced contraction frequency without affecting amplitude	China	[336]
Human myometrial tissue, pregnant rat myometrium	Mediates L-type calcium channels and K_{ATP} channels, reducing Ca^{2+} influx	Inhibits myometrial contractions, maintaining uterine stability during pregnancy	UK	[337]

Sulfatonic®

Table 1 (continued)

Disease type, H_2S donor, Chemical type Research model	Mechanism of action	Key effects & findings	Country	Reference
Uterine smooth muscle cells (UMSCs), LPS-induced preterm labor mouse model	Inhibits TLR4/NF-κB signaling and blocks NLRP3 inflammasome activation	Reduces uterine CAPs and pro-inflammatory cytokine expression, delaying LPS-induced preterm labor	China	[333]
Pregnant rat myometrium	Relaxes smooth muscle, reduces contraction strength	NaHS and L-cysteine dose-dependently inhibit spontaneous contractions in rat uterine smooth muscle	UK	[335]
LPS-induced preterm labor mouse model	Downregulates ERK1/2 and NF-κB signaling, inhibits pro-inflammatory cytokines, prevents leukocyte infiltration	Maintains uterine quiescence during infection/inflammation	China	[334]
Human and pregnant rat myometrial tissue GYY4137 Organic slow-releasing donor	Mediates L-type calcium channels and K_{ATP} channels, reducing Ca^{2+} influx	Reduces CAPs production in myometrial cells by decreasing inflammatory cytokine expression	China	[214]
Human and pregnant rat myometrial tissue Na_2S Inorganic salt (fast-releasing donor)	Mediates L-type calcium channels and K_{ATP} channels, reducing Ca^{2+} influx	Inhibits myometrial contractions	UK	[337]
Rat uterine tissue ATB-346 H_2S-releasing naproxen derivative	Mediated through a DIDS-sensitive Cl^- channel pathway, influenced by redox status and Ca^{2+} levels	Induces relaxation of uterine smooth muscle cells	Serbia	[338]
Human myometrial tissue RSA NaHS Inorganic salt (fast-releasing donor)	Releases H_2S while activating endogenous H_2S to relax smooth muscle, with COX inhibition reducing inflammation	More effectively reduces uterine contraction amplitude and total contractile force compared to Na_2S	UK Serbia	[339]
Pregnant mouse model GYY4137 Organic slow-releasing donor	Restores TGF-β and PGE2 levels, balances Th1/Th2 immunity, inhibits NF-κB, reduces IL-1R1 and COX2 expression	Rapidly alleviates inflammation, enhances immune tolerance, reduces pregnancy loss	China	[24]
HTR8/SVneo JEG3	Upregulates MMP-2 and VEGF expression	Enhances trophoblast migration and invasion in a dose-dependent manner	China	[24]
Pregnant mouse model FGR DATS Organic sulfur compound	Long-term inhibition of the NF-κB pathway to prevent excessive activation of COX2 and PGE2; Reduction of pro-inflammatory factors TNF-α and IFN-γ; Maintenance of Th1/Th2 balance and sustained promotion of TGF-β expression	Long-term immune homeostasis maintenance, suppression of chronic inflammation, enhancement of maternal-fetal immune tolerance, and prevention of recurrent miscarriage	China	[24]
Human placental tissue NaHS Inorganic salt (fast-releasing donor)	Upregulates MHC, SMA, desmin, and CRBP1	Promotes SMC differentiation and stability, prevents abnormal vascular remodeling, optimizes placental blood flow in FGR	UK	[351]

Sulfatonic®

Table 1 (continued)

Disease type, H_2S donor, Chemical type Research model	Mechanism of action	Key effects & findings	Country	Reference
Human placental tissue	Activates K_{ATP} channels, enhances NOS activity, promotes vasodilation	Improves placental perfusion, protects fetal growth in pregnancy complications	UK	[163]
GYY4137				
Organic slow-releasing donor				
Pregnant rat model	Reduces hypertension-induced placental oxidative stress	Improves placental function, significantly increases placental and fetal weight	Brazil	[352]

H2S hydrogen sulfide, *PE* preeclampsia, *KATP* activating adenosine triphosphate (ATP)-sensitive K + channel, *RVLM* rostral ventrolateral medulla *LPS* lipopolysaccharide, *HUVECs* human umbilical vein endothelial cells, *sFlt-1* soluble fms-like tyrosine kinase-1, *sEng* soluble endoglin, *Bcl-2* B-cell lymphoma-2, *PRAP* proline-rich acidic protein, *MMP* matrix metalloproteinase, *TIMP* tissue inhibitor of metalloproteinases, *H/R* hypoxia/reoxygenation, *MAPK* mitogen-activated protein kinase, *RIPA1* receptor-interacting serine/threonine-kinase-1, *RIPK3* receptor-interacting serine/threonine-kinase-3, *eNOS* endothelial nitric oxide synthase, *RI* resistance index, *PI* pulsatility index, *MTFR1L* mitochondrial fission regulator 1-like protein, *Miro2* mitochondrial Rho GTPase 2, *GDM* gestational diabetes mellitus, *NLRP3* nucleotide-binding oligomerization domain-like receptor 3, *UMSCs* Uterine smooth muscle cells, *TLR4* Toll-like receptor 4, *NF-κB* nuclear factor-kappa B, *CAPs* contraction-associated proteins, *ERK1/2* extracellular signal regulated kinase, *COX* cyclooxygenase, *Th1: T-helper 1* Th2: T- helper 2, *VEGF* vascular endothelial growth factor, *PGE2* prostaglandin-E2, *FGR* fetal growth restriction, *MHC* myosin heavy chain, *SMA* smooth muscle actin, *CRBP1* cellular retinol-binding protein 1

p38 MAPK signaling pathway. In mouse experiments, supplementation chondroitin sulfate increased SRB (e.g., *Desulfovibrio piger*), enhanced colonic H_2S production, and improved glucose tolerance through elevated GLP-1 and insulin secretion. These findings highlight the potential of H_2S donors or microbiota-targeted prebiotics as novel antidiabetic strategies.

GDM, defined as glucose intolerance first diagnosed during pregnancy, is primarily driven by IR and insufficient β-cell compensation [317]. While often considered transient, GDM is a strong predictor of future type 2 diabetes mellitus and has long-term health implications for both mother and child [317–320]. Emerging evidence indicates that H_2S deficiency may contribute to GDM pathogenesis. Teng et al. [321] observed significantly reduced peripheral blood H_2S levels in GDM patients. Inflammatory cytokines such as IL-6 and TNF-α are elevated in GDM, correlating positively blood glucose and negatively with H_2S levels, suggesting that H_2S may modulate GDM by suppressing inflammation [321, 322]. Moreover, placental and adipose-derived cytokines such as IL-1β and IL-18 exacerbate maternal IR [323–325], and the nucleotide-binding oligomerization domain-like receptor 3 (NLRP3) inflammasome plays a central role in this inflammatory response [326, 327]. Studies by Zhang et al. [328] and Wu et al. [329] demonstrated upregulation of NLRP3 and caspase-1 in GDM placentas, along with decreased expression of H_2S-synthesizing enzymes (CSE and CBS). Wu et al. further show that NaHS or its precursor Cys inhibited NLRP3 signaling and decreased IL-1β and IL-18 production in human placental cells [329]. These findings suggest that H_2S may alleviate placental inflammation and maternal IR by modulating the NLRP3 inflammasome. The anti-inflammatory, antioxidant, and antiapoptotic properties of H_2S [306, 330] further support its therapeutic potential in GDM.

However, current research remains at an early stage. Existing studies have focused primarily on animal models or in vitro experiments, and key mechanisms—such as H_2S involvement in insulin signaling, glucose transport, gut microbiota, and placental function, require further elucidation. Notably, the placenta plays a crucial role in maternal–fetal metabolic regulation by secreting cytokines and hormones that influence IR [331, 332]. Dysfunction placental signaling may intensify systemic inflammation and worsen metabolic homeostasis in GDM. Although H_2S is essential for placental development, its potential role in modulating early placental function during GDM pathogenesis remains largely unexplored. Further investigation into this axis could offer new insights into GDM prevention, early screening, and targeted intervention strategies.

PTB

Uterine quiescence is essential for maintaining pregnancy to term. H_2S production increases during pregnancy but drops sharply at labor onset [170], suggesting its pivotal role in preventing PTB [69, 214]. Infection and inflammation are major triggers of preterm labor and H_2S has been shown to suppress uterine inflammation by inhibiting the TLR4/NF-κB pathway, thereby downregulating NLRP3 inflammasome activation, contraction-associated proteins and proinflammatory cytokines in human myometrial tissue [333]. In mouse models, NaHS delays lipopolysaccharide (LPS)-induced PTB by dampening inflammatory signaling [96, 334]. Nonetheless, the role of H_2S in inflammation-associated PTB may vary depending on the underlying stimuli. H_2S also exerts tocolytic effects by relaxing uterine smooth muscle. In pregnant rats, both NaHS and its precursor cysteine dose-dependently inhibited spontaneous myometrial contractions [335]. Similar effects were observed in human myometrial tissue, where NaHS reduced contraction amplitude

and frequency in a dose-dependent manner [336]. Robinson et al. [337] reported that both GYY4137 and NaHS significantly suppressed oxytocin- and high K^+-induced contractions in pregnant rat and human myometrial tissue, mainly via L-type calcium and K_{ATP} channels.

Anti-inflammatory actions of H_2S further contribute to uterine quiescence. You et al. [214] demonstrated that in human uterine SMCs, both the H_2S donor NaHS and its precursor Cys inhibited NF-κB activation and proinflammatory cytokine production, thereby reducing CAP expression. Chen et al. [333] also reported that NaHS downregulated CAP expression by inhibiting the TLR4/NF-κB/NLRP3 axis. In vivo, NaHS delayed LPS-induced PTB in mice by reducing leukocyte infiltration and inhibiting ERK1/2 and NF-κB pathways [334].

Other mechanisms have also been implicated. Na_2S-induced uterine relaxation involves DIDS-sensitive Cl^- channels and redox- and Ca^{2+}-mediated pathways [338]. A recent study discovered that ATB-346, a novel H_2S-releasing compound, exhibited a stronger uterine relaxation effect than Na_2S, naproxen, or TBZ at the same concentration did, significantly reducing the contraction amplitude and total contractile force [339].

Collectively, H_2S plays a multifaceted role in maintaining uterine quiescence by suppressing inflammation and regulating uterine smooth muscle. Donors such as NaHS, GYY4137, and ATB-346 show promise as tocolytics. However, theirpharmacokinetics, safety, and efficacy require further optimization and clinical validation.

RSA

RSA, defined as three or more consecutive miscarriages before 20–28 weeks of gestation [340], affects approximately 5% of reproductive-age couples worldwide [341]. Notably, about 60% of cases are classified as unexplained recurrent spontaneous abortion (URSA), with immune dysregulation at the maternal–fetal interface considered a key pathogenic factor [342, 343]. During implantation, inflammatory cues trigger a maternal immune shift from a Th1- to a Th2-dominant state, essential for immune tolerance throughout pregnancy [207, 344]. H_2S promotes regulatory T cells (Tregs) differentiation, thereby enhancing immune tolerance to fetal antigens [345, 346]. Wang et al. [24] reported that placental CBS expression was significantly reduced in URSA patients compared to normal pregnancies, while CSE levels remained unchanged. In mouse models, CBS deficiency led to increased embryo resorption and a Th1/Th2 imbalance in decidual tissues. Importantly, exogenous H_2S donors (NaHS or GYY4137) partially reversed early pregnancy loss in both $CBS^{+/-}$ maternal mice and the CBA/J × DBA/2 RSA model mice, suggesting therapeutic value in immune-mediated RSA.

Impaired trophoblast invasion is another contributor to RSA, as failure to remodel maternal spiral arteries can lead to placental insufficiency and pregnancy failure [347]. Wang et al. [24] demonstrated that NaHS enhanced trophoblast migration and invasion in HTR8/SVneo and JEG3 cells, accompanied by increased MMP-2 and VEGF expression-effects similar to CBS overexpression. Transcriptomic analysis further revealed CBS-dependent changes in immune and inflammatory responses, including IL-1R and prostaglandin-endoperoxide synthase 2, both involved in NF-κB-mediated inflammatory signaling. These findings suggest that H_2S donors not only enhance trophoblast migration and invasion but also modulate inflammation and immune balance at the maternal–fetal interface, supporting their potential role in improving immune tolerance and reducing the risk of RSA.

FGR

FGR is a major contributor to adverse perinatal outcomes, including intrauterine fetal death, neonatal asphyxia, and hypoxemia. Moreover, FGR has long-term consequences, increasing the risk of cognitive developmental delays in childhood and metabolic disorders such as type 2 diabetes and cardiovascular diseases in adulthood [348]. Approximately 65–70% of FGR cases present with abnormal umbilical artery Doppler waveforms [349], reflecting placental hypoperfusion and increased placental vascular resistance, which are central to FGR pathogenesis [349, 350]. Cindrova-Davies et al. [163] found that CSE expression in trophoblasts from FGR and PE placentas with abnormal Doppler flow, which correlated with increased placental vascular resistance, implicating CSE/H_2S dysregulation in impaired perfusion. In human placental tissues precontracted with thromboxane mimetics, NaHS induced vasodilation by activating K_{ATP} channels and enhancing NOS activity, thus improving blood flow. Lu et al. [351] further characterized vascular remodeling in stem villous arteries of FGR placentas, noting decreased expression of contractile markers, including myosin heavy chain, smooth muscle actin, and desmin, and elevated dedifferentiation markers such as cellular retinol-binding protein 1 (CRBP1) and MMP-2. These changes were accompanied by lumen narrowing and increased wall thickness-to-lumen ratio. CSE expression positively correlated with contractile markers and birth weight, while CRBP1 and MMP-2 showed inverse correlations. In vitro, hypoxia-reoxygenation or CSE inhibition recapitulated these structural abnormalities, whereas treatment with the H_2S donor DATS prevented pathological remodeling, suggesting that H_2S supports vascular integrity by maintaining SMC differentiation. Zochio et al. [352] investigated that GYY4137, a slow-releasing H_2S donor, improved placental functionin hypertensive pregnancy models, increasing placental and fetal weights while reducing oxidative stress. These

findings further support the potential of GYY4137 in placental dysfunction associated with FGR by improving placental perfusion, alleviating oxidative stress, and stabilizing the placental microenvironment.

Overall, H_2S appears to be a key regulator of placental perfusion, vascular remodeling, and oxidative stress control. H_2S donors such as GYY4137 and DATS show therapeutic promise in improving placental function and promoting fetal growth. However, most findings are preclinical; robust clinical studies are needed to evaluate safety, efficacy, and optimal delivery strategies to guide potential translation into FGR therapies.

Co-Therapeutic potential of H_2S donors: exploring combined treatment strategies

H_2S and CO are both endogenous gaseous signaling molecules with overlapping biological activities, including vasodilation, anti-inflammation, and cytoprotection. This functional similarity has prompted the development of dual-donor compounds capable of simultaneously releasing H_2S and CO. Bai et al. first synthesized such CO-H_2S dual-donors, which exhibited enhanced bioactivity and significant anti-proliferative effects [353]. These compounds also demonstrated anti-inflammatory, antihypertensive, and cardioprotective properties. However, at higher concentrations (> 10 μmol·L^{-1}), they caused developmental malformations in zebrafish embryos, highlighting the need for careful evaluation of their pharmacological profiles and safety.

The combined application of H_2S and NO donors has also attracted growing attention. NO is a well-established vasodilator that supports vascular tone, inhibits platelet aggregation, and enhances microcirculation. By combining NO and H_2S donors, researchers aim to leverage their synergistic effects, particularly in vascular protection and oxidative stress reduction during pregnancy. For example, Wang et al. [354] synthesized NOSH-NBP-5, a dual-donor compound integrating butylphthalide (a neuroprotective agent), NO and H_2S. Similarly, Kodela et al. [355] developed dual-donor aspirin derivatives (NOSH-1 to NOSH-4), which simultaneously release NO and H_2S. These compounds exhibit potent anticancer activity, particularly NOSH-1, which had an IC_{50} of (48 ± 3) nmol·L^{-1} against colorectal cancer cells (HT-29), which is significantly lower than that of aspirin (IC_{50} >5 mmol·L^{-1}), indicating that the combination of NO and H_2S donors could greatly enhance the therapeutic efficacy of conventional drugs.

Although current research has focused primarily on cancer, cardiovascular diseases, and neuroprotection, H_2S-NO and H_2S–CO dual donors show synergistic anti-inflammatory, antioxidant, and vasodilatory effects that could be highly relevant for pregnancy complications. These include modulation of inflammation at the maternal–fetal interface, enhancement of placental perfusion, and amelioration of vascular dysfunction in pregnancy-induced hypertension and PE. However, studies on dual gasotransmitter donors in the context of pregnancy remain scarce, and many lack comprehensive assessments of pharmacokinetics, long-term safety, and translational feasibility. Future research should focus on integrating in vivo models, ex vivo placental systems, and clinical trials to validate the therapeutic potential of H_2S-based combination strategies in maternal–fetal medicine.

Conclusions

H_2S, an essential endogenous gasotransmitter, plays multifaceted roles in placental development by regulating trophoblast invasion, angiogenesis, vascular remodeling, and immune homeostasis. Emerging evidence indicates that dysregulated H_2S production is closely associated with pregnancy-related complications such as PE, FGR, and PTB. Preclinical studies suggest that H_2S donors can improve placental perfusion and alleviate vascular dysfunction, highlighting their therapeutic potential. However, clinical translation remains limited by challenges in targeted delivery, dosing, and safety. Future efforts should focus on developing stable, tissue-specific H_2S-releasing compounds, clarifying molecular mechanisms, and exploring synergy with other gasotransmitters like NO and CO. Clinical trials and biomarker-driven strategies are needed to validate efficacy and enable personalized interventions. H_2S-based therapies hold promise as innovative approaches for preventing and treating pregnancy-related disorders, with further research critical to advancing their clinical application.

Abbreviations

UA	Uterine artery
SAR	Spiral artery remodeling
EVT	Extravillous trophoblast
SMC	Smooth muscle cell
PE	Preeclampsia
FGR	Fetal growth restriction
RSA	Recurrent spontaneous abortion
PTB	Preterm birth
H_2S	Hydrogen sulfide
NO	Nitric oxide
CO	Carbon monoxide
K_{ATP}	Activating adenosine triphosphate (ATP)-sensitive K^+ channels
BK_{Ca}	Large-conductance calcium-activated potassium channels
VEGF	Vascular endothelial growth factor
CBS	Cystathionine β-synthase
CSE	Cystathionine γ-lyase
3-MST	3-mercaptopyruvate sulfurtransferase
UtBF	Uterine blood flow
PLP	Pyridoxal-5′-phosphate
Hcy	Homocysteine
Ser	Serine
Cth	Cystathionine
PlGF	Placental growth factor
MAPK	Mitogen-activated protein kinases
$ONOO^-$	Peroxynitrite
NO_2^-	Nitrite
3-MP	3-mercaptopyruvate

CAT	Cysteine aminotransferase
SSH	Persulfides
DAO	D-amino acid oxidase
Cys	L-cysteine
SRB	Sulfate-reducing bacteria
SO_4^{2-}	Utilizing sulfate
S^{2-}	Sulfide
SO_3^{2-}	Sulfite
$S_2O_3^{2-}$	Thiosulfate
DATS	Diallyl trisulfide
GSH	Glutathione
Fe^{3+}	Ferric iron
SQR	Sulfide quinone oxidoreductase
ETHE1	Persulfide dioxygenase
SUOX	Sulfite oxidase
SO_4^{2-}	Sulfate
SO_4^{2-}	Sulfate
TST	Thiosulfate sulfurtransferase
$S_2O_3^{2-}$	Thiosulfate
CH_3SH	Methanethiol
S-Hb	Sulf-hemoglobin
$HSxS^-$	Polysulfides
CTBs	Cytotrophoblasts
STBs	Syncytiotrophoblasts
ECs	Endothelial cells
uNK	Uterine natural killer
MMPs	Matrix metalloproteinases
sGC	Soluble guanylate cyclase
sFlt-1	Soluble fms-like tyrosine kinase-1
sEng	Soluble endoglin
IUGR	Intrauterine growth restriction
MTFR1L	Mitochondrial fission regulator 1-like protein
TLR4	Toll-like receptor 4
VSMCs	Vascular smooth muscle cells
eNOS	Endothelial nitric oxide synthase
ERK1/2	Extracellular signal regulated kinase
HO-1	Heme oxygenase-1
Th1	T-helper 1
Th2	T-helper 2
NF-κB	Nuclear factor-kappa B
H/R	Hypoxia/reoxygenation
E1	Estrone
E2	Estradiol
E3	Estriol
E4	Estetrol
OVX	Ovariectomized
ERs	Estrogen receptors
GPER	G protein-coupled estrogen receptor
cGMP	Cyclic guanosine monophosphate
TFs	Transcription factors
EREs	Estrogen response elements
pGC-A	Particulate guanylate cyclase A
PKG-I	CGMP-dependent protein kinase I
GDM	Gestational diabetes mellitus
HFD	High-fat diet
IR	Insulin resistance
GLP-1	Glucagon-like peptide-1
NLRP3	Nucleotide-binding oligomerization domain-like receptor 3
LPS	Lipopolysaccharide
URSA	Inexplained recurrent spontaneous abortion
CRBP1	Cellular retinol-binding protein 1

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01465-1.

Supplementary Material 1.

Acknowledgements
Not applicable.

Authors' contributions
LD and ZY conceived the study, drafted the initial manuscript, and—together with RZ—led the major revisions. RZ was added as a co–first author in recognition of her substantial contributions during the revision process. LD, YL, and RZ conducted the literature review and prepared the figures. WR, YL, and XZ collected the data and contributed to manuscript editing. ZY and SC supervised the study and provided final approval. All authors critically reviewed and approved the final version of the manuscript.

Funding
The authors acknowledge financial support from the Hebei Natural Science Foundation (Grant No. H2022206600, H2022206212); National Natural Science Foundation of China(Grant No. 32471044); the Research and Innovation Team of the Fourth Hospital of Hebei Medical University (Grant No. 2023C04); the Government-Funded Program for Training Outstanding Clinical Medical Talents (Grant No. ZF2025212);the Medical Science Research Project of Hebei (Grant No. 20240817).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Obstetrical Department, the Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China
[2]Department of Histology and Embryology, College of Basic Medical, Hebei Medical University, Shijiazhuang, China

Received: 17 April 2025 / Accepted: 10 August 2025
Published online: 30 September 2025

References

1. Burton GJ, Fowden AL. The placenta: a multifaceted, transient organ. Philos Trans R Soc Lond B Biol Sci. 2015;370(1663):20140066.
2. Aplin JD, Myers JE, Timms K, Westwood M. Tracking placental development in health and disease. Nat Rev Endocrinol. 2020;16(9):479–94.
3. Rosenfeld CR, Morriss FH Jr., Makowski EL, Meschia G, Battaglia FC. Circulatory changes in the reproductive tissues of Ewes during pregnancy. Gynecol Invest. 1974;5(5–6):252–68.
4. Osol G, Mandala M. Maternal uterine vascular remodeling during pregnancy. Physiol (Bethesda). 2009;24:58–71.
5. Myatt L. Control of vascular resistance in the human placenta. Placenta. 1992;13(4):329–41.
6. Spradley FT, Ge Y, Granger JP, Chade AR. Utero-placental vascular remodeling during late gestation in Sprague-Dawley rats. Pregnancy Hypertens. 2020;20:36–43.
7. Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. J Pathol Bacteriol. 1967;93(2):569–79.
8. Turco MY, Moffett A. Development of the human placenta. Development. 2019;146(22).dev163428.
9. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta. 2006;27(9–10):939–58.
10. Espinoza J, Romero R, Mee Kim Y, Kusanovic JP, Hassan S, Erez O, Gotsch F, Than NG, Papp Z, Jai Kim C. Normal and abnormal transformation of the spiral arteries during pregnancy. J Perinat Med. 2006;34(6):447–58.

Sulfatonic®

11. Allerkamp HH, Clark AR, Lee TC, Morgan TK, Burton GJ, James JL. Something old, something new: digital quantification of uterine vascular remodelling and trophoblast plugging in historical collections provides new insight into adaptation of the utero-placental circulation. Hum Reprod. 2021;36(3):571–86.
12. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The great obstetrical syndromes are associated with disorders of deep placentation. Am J Obstet Gynecol. 2011;204(3):193–201.
13. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30(6):473–82.
14. Qi QR, Lechuga TJ, Patel B, Nguyen NA, Yang YH, Li Y, Sarnthiyakul S, Zhang QW, Bai J, Makhoul J, et al. Enhanced stromal cell CBS-H2S production promotes Estrogen-Stimulated human endometrial angiogenesis. Endocrinology. 2020;161(11):bqaa176.
15. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.
16. Torres-Torres J, Espino YSS, Martinez-Portilla R, Borboa-Olivares H, Estrada-Gutierrez G, Acevedo-Gallegos S, Ruiz-Ramirez E, Velasco-Espin M, Cerda-Flores P, Ramirez-Gonzalez A et al. A narrative review on the pathophysiology of preeclampsia. Int J Mol Sci. 2024;25(14):7569.
17. Liu Y, Du L, Gu S, Liang J, Huang M, Huang L, Lai S, Zhang S, Tu Z, Sun W, et al. Identification of the role of DAB2 and CXCL8 in uterine spiral artery remodeling in early-onset preeclampsia. Cell Mol Life Sci. 2024;81(1):180.
18. Gupta SK, Mochan S, Arora P, Rani N, Luthra K, Dwivedi S, Bhatla N, Kshetrapal P, Dhingra R. Hydrogen sulfide promotes migration of trophoblast cells by a Rho GTPase mediated actin cytoskeleton reorganization. Placenta. 2023;142:135–46.
19. Cui J, Yang Z, Ma R, He W, Tao H, Li Y, Zhao Y. Placenta-targeted treatment strategies for preeclampsia and fetal growth restriction: an opportunity and major challenge. Stem Cell Rev Rep. 2024;20(6):1501–11.
20. Brouwers L, de Gier S, Vogelvang TE, Veerbeek JHW, Franx A, van Rijn BB, Nikkels PGJ. Prevalence of placental bed spiral artery pathology in pre-eclampsia and fetal growth restriction: A prospective cohort study. Placenta. 2024;156:1–9.
21. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018;218(2s):S745–61.
22. Khong TY, Liddell HS, Robertson WB. Defective haemochorial placentation as a cause of miscarriage: a preliminary study. Br J Obstet Gynaecol. 1987;94(7):649–55.
23. Ball E, Bulmer JN, Ayis S, Lyall F, Robson SC. Late sporadic miscarriage is associated with abnormalities in spiral artery transformation and trophoblast invasion. J Pathol. 2006;208(4):535–42.
24. Wang B, Xu T, Li Y, Wang W, Lyu C, Luo D, Yang Q, Ning N, Chen ZJ, Yan J, et al. Trophoblast H2S maintains early pregnancy via regulating Maternal-Fetal interface immune hemostasis. J Clin Endocrinol Metab. 2020;105(12):e4275–4289.
25. Liu X, Aneas I, Sakabe N, Anderson RL, Billstrand C, Paz C, Kaur H, Furner B, Choi S, Prichina AY, et al. Single cell profiling at the maternal-fetal interface reveals a deficiency of PD-L1(+) non-immune cells in human spontaneous preterm labor. Sci Rep. 2023;13(1):7903.
26. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation. 2011;123(24):2856–69.
27. Weissgerber TL, Mudd LM. Preeclampsia and diabetes. Curr Diab Rep. 2015;15(3):9.
28. Cohen E, Wong FY, Horne RS, Yiallourou SR. Intrauterine growth restriction: impact on cardiovascular development and function throughout infancy. Pediatr Res. 2016;79(6):821–30.
29. Burton GJ, Fowden AL, Thornburg KL. Placental origins of chronic disease. Physiol Rev. 2016;96(4):1509–65.
30. Lee EY, Chang CY, Hu N, Wang YC, Lai CC, Herrup K, Lee WH, Bradley A. Mice deficient for Rb are nonviable and show defects in neurogenesis and haematopoiesis. Nature. 1992;359(6393):288–94.
31. Clarke AR, Maandag ER, van Roon M, van der Lugt NM, van der Valk M, Hooper ML. Berns A, Te Riele H: requirement for a functional Rb-1 gene in murine development. Nature. 1992;359(6393):328–30.
32. Davis AC, Wims M, Spotts GD, Hann SR, Bradley A. A null c-myc mutation causes lethality before 10.5 days of gestation in homozygotes and reduced fertility in heterozygous female mice. Genes Dev. 1993;7(4):671–82.
33. Wu L, de Bruin A, Saavedra HI, Starovic M, Trimboli A, Yang Y, Opavska J, Wilson P, Thompson JC, Ostrowski MC, et al. Extra-embryonic function of Rb is essential for embryonic development and viability. Nature. 2003;421(6926):942–7.
34. Dubois NC, Adolphe C, Ehninger A, Wang RA, Robertson EJ, Trumpp A. Placental rescue reveals a sole requirement for c-Myc in embryonic erythroblast survival and hematopoietic stem cell function. Development. 2008;135(14):2455–65.
35. Perez-Garcia V, Fineberg E, Wilson R, Murray A, Mazzeo CI, Tudor C, Sienerth A, White JK, Tuck E, Ryder EJ, et al. Placentation defects are highly prevalent in embryonic lethal mouse mutants. Nature. 2018;555(7697):463–8.
36. Adams RH, Porras A, Alonso G, Jones M, Vintersten K, Panelli S, Valladares A, Perez L, Klein R, Nebreda AR. Essential role of p38alpha MAP kinase in placental but not embryonic cardiovascular development. Mol Cell. 2000;6(1):109–16.
37. Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A, Evans RM. PPAR gamma is required for placental, cardiac, and adipose tissue development. Mol Cell. 1999;4(4):585–95.
38. O'Keeffe GW, Kenny LC. Predicting infant neurodevelopmental outcomes using the placenta? Trends Mol Med. 2014;20(6):303–5.
39. Hodyl NA, Aboustate N, Bianco-Miotto T, Roberts CT, Clifton VL, Stark MJ. Child neurodevelopmental outcomes following preterm and term birth: what can the placenta tell us? Placenta. 2017;57:79–86.
40. Maltepe E, Fisher SJ. Placenta: the forgotten organ. Annu Rev Cell Dev Biol. 2015;31:523–52.
41. Bonnin A, Goeden N, Chen K, Wilson ML, King J, Shih JC, Blakely RD, Deneris ES, Levitt P. A transient placental source of serotonin for the fetal forebrain. Nature. 2011;472(7343):347–50.
42. Ho L, van Dijk M, Chye STJ, Messerschmidt DM, Chng SC, Ong S, Yi LK, Boussata S, Goh GH, Afink GB, et al. ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice. Science. 2017;357(6352):707–13.
43. Jones HN, Olbrych SK, Smith KL, Cnota JF, Habli M, Ramos-Gonzales O, Owens KJ, Hinton AC, Polzin WJ, Muglia LJ, et al. Hypoplastic left heart syndrome is associated with structural and vascular placental abnormalities and leptin dysregulation. Placenta. 2015;36(10):1078–86.
44. Matthiesen NB, Henriksen TB, Agergaard P, Gaynor JW, Bach CC, Hjortdal VE, Østergaard JR. Congenital heart defects and indices of placental and fetal growth in a nationwide study of 924 422 liveborn infants. Circulation. 2016;134(20):1546–56.
45. Rychik J, Goff D, McKay E, Mott A, Tian Z, Licht DJ, Gaynor JW. Characterization of the placenta in the newborn with congenital heart disease: distinctions based on type of cardiac malformation. Pediatr Cardiol. 2018;39(6):1165–71.
46. Hosoki R, Matsuki N, Kimura H. The possible role of hydrogen sulfide as an endogenous smooth muscle relaxant in synergy with nitric oxide. Biochem Biophys Res Commun. 1997;237(3):527–31.
47. Van Buren GA, Yang DS, Clark KE. Estrogen-induced uterine vasodilatation is antagonized by L-nitroarginine Methyl ester, an inhibitor of nitric oxide synthesis. Am J Obstet Gynecol. 1992;167(3):828–33.
48. Tschugguel W, Stonek F, Zhegu Z, Dietrich W, Schneeberger C, Stimpfl T, Waldhoer T, Vycudilik W, Huber JC. Estrogen increases endothelial carbon monoxide, Heme Oxygenase 2, and carbon monoxide-derived cGMP by a receptor-mediated system. J Clin Endocrinol Metab. 2001;86(8):3833–9.
49. Chen DB, Feng L, Hodges JK, Lechuga TJ, Zhang H. Human trophoblast-derived hydrogen sulfide stimulates placental artery endothelial cell angiogenesis. Biol Reprod. 2017;97(3):478–89.
50. Macabrey D, Joniová J, Gasser Q, Bechelli C, Longchamp A, Urfer S, Lambelet M, Fu CY, Schwarz G, Wagnières G, et al. Sodium thiosulfate, a source of hydrogen sulfide, stimulates endothelial cell proliferation and neovascularization. Front Cardiovasc Med. 2022;9:965965.
51. Bai J, Jiao F, Salmeron AG, Xu S, Xian M, Huang L, Chen DB. Mapping Pregnancy-dependent sulfhydrome unfolds diverse functions of protein sulfhydration in human uterine artery. Endocrinology. 2023;164(9):bqad107.
52. Mustafa AK, Sikka G, Gazi SK, Steppan J, Jung SM, Bhunia AK, Barodka VM, Gazi FK, Barrow RK, Wang R, et al. Hydrogen sulfide as endothelium-derived hyperpolarizing factor sulfhydrates potassium channels. Circ Res. 2011;109(11):1259–68.
53. Lv B, Chen S, Tang C, Jin H, Du J, Huang Y. Hydrogen sulfide and vascular regulation - An update. J Adv Res. 2021;27:85–97.
54. Li Y, Bai J, Yang YH, Hoshi N, Chen DB. Hydrogen sulfide relaxes human uterine artery via activating smooth muscle BK(Ca) channels. Antioxidants (Basel). 2020;9(11):1127.
55. Munteanu C, Popescu C, Vlădulescu-Trandafir AI, Onose G. Signaling Paradigms of H(2)S-Induced Vasodilation: A Comprehensive Review. Antioxidants (Basel). 2024;13(10):1158.

56. Altaany Z, Yang G, Wang R. Crosstalk between hydrogen sulfide and nitric oxide in endothelial cells. J Cell Mol Med. 2013;17(7):879–88.
57. Hu TX, Wang G, Guo XJ, Sun QQ, He P, Gu H, Huang Y, Gao L, Ni X. MiR 20a,-20b and – 200c are involved in hydrogen sulfide stimulation of VEGF production in human placental trophoblasts. Placenta. 2016;39:101–10.
58. Zhang HH, Chen JC, Sheibani L, Lechuga TJ, Chen DB. Pregnancy augments VEGF-Stimulated in vitro angiogenesis and vasodilator (NO and H2S) production in human uterine artery endothelial cells. J Clin Endocrinol Metab. 2017;102(7):2382–93.
59. Smith GC. First-trimester determination of complications of late pregnancy. JAMA. 2010;303(6):561–2.
60. Arutyunyan A, Roberts K, Troulé K, Wong FCK, Sheridan MA, Kats I, Garcia-Alonso L, Velten B, Hoo R, Ruiz-Morales ER, et al. Spatial multiomics map of trophoblast development in early pregnancy. Nature. 2023;616(7955):143–51.
61. Araujo-Alvarez JM, Trujillo-Ferrara JG. [De Morbis artificum diatriba. 1700–2000.]. Salud Publica Mex. 2002;44(4):362–70.
62. Santana Maldonado C, Weir A, Rumbeiha WK. A comprehensive review of treatments for hydrogen sulfide poisoning: past, present, and future. Toxicol Mech Methods. 2023;33(3):183–96.
63. Abe K, Kimura H. The possible role of hydrogen sulfide as an endogenous neuromodulator. J Neurosci. 1996;16(3):1066–71.
64. Zhao W, Zhang J, Lu Y, Wang R. The vasorelaxant effect of H(2)S as a novel endogenous gaseous K(ATP) channel opener. Embo J. 2001;20(21):6008–16.
65. Paul BD, Snyder SH. H2S: A novel Gasotransmitter that signals by sulfhydration. Trends Biochem Sci. 2015;40(11):687–700.
66. Sun X, Zhang R, Zhong Q, Song Y, Feng X. Regulatory effects of hydrogen sulfide on the female reproductive system. Eur J Pharmacol. 2024;963:176265.
67. Song Y, Mao C, Zhong Q, Zhang R, Jiang D, Sun X. Role of hydrogen sulfide in the male reproductive system. Front Endocrinol (Lausanne). 2024;15:1377090.
68. Guerra DD, Hurt KJ. Gasotransmitters in pregnancy: from conception to uterine Involution. Biol Reprod. 2019;101(1):4–25.
69. Pilsova A, Pilsova Z, Klusackova B, Zelenkova N, Chmelikova E, Postlerova P, Sedmikova M. Hydrogen sulfide and its role in female reproduction. Front Vet Sci. 2024;11:1378435.
70. Lechuga TJ, Qi QR, Magness RR, Chen DB. Ovine uterine artery hydrogen sulfide biosynthesis in vivo: effects of ovarian cycle and pregnancy†. Biol Reprod. 2019;100(6):1630–6.
71. Sheibani L, Lechuga TJ, Zhang H, Hameed A, Wing DA, Kumar S, Rosenfeld CR, Chen DB. Augmented H2S production via cystathionine-beta-synthase upregulation plays a role in pregnancy-associated uterine vasodilation. Biol Reprod. 2017;96(3):664–72.
72. Robert K, Vialard F, Thiery E, Toyama K, Sinet PM, Janel N, London J. Expression of the cystathionine beta synthase (CBS) gene during mouse development and immunolocalization in adult brain. J Histochem Cytochem. 2003;51(3):363–71.
73. Wang Z, Liu DX, Wang FW, Zhang Q, Du ZX, Zhan JM, Yuan QH, Ling EA, Hao AJ. L-Cysteine promotes the proliferation and differentiation of neural stem cells via the CBS/H_2S pathway. Neuroscience. 2013;237:106–17.
74. Kimura H. Signaling molecules: hydrogen sulfide and polysulfide. Antioxid Redox Signal. 2015;22(5):362–76.
75. Zuhra K, Augsburger F, Majtan T, Szabo C. Cystathionine-β-Synthase: molecular regulation and Pharmacological Inhibition. Biomolecules. 2020;10(5):697.
76. Filipovic MR, Zivanovic J, Alvarez B, Banerjee R. Chemical biology of H(2)S signaling through persulfidation. Chem Rev. 2018;118(3):1253–337.
77. Shahid A, Bhatia M. Hydrogen sulfide: A versatile molecule and therapeutic target in health and diseases. Biomolecules. 2024;14(9):1145.
78. Lechuga TJ, Qi QR, Kim T, Magness RR, Chen DB. E2β stimulates ovine uterine artery endothelial cell H2S production in vitro by Estrogen receptor-dependent upregulation of cystathionine β-synthase and cystathionine γ-lyase expression†. Biol Reprod. 2019;100(2):514–22.
79. Abu-Ghazaleh N, Brennecke S, Murthi P, Karanam V. Association of vascular endothelial growth factors (VEGFs) with recurrent miscarriage: A systematic review of the literature. Int J Mol Sci. 2023;24(11):9449.
80. Pinilla JM, Ayala-Ramírez P, García-Robles R, Olaya CM, Bermúdez M. Expression of cystathionine beta-synthase and histopathological observations in placentas of patients with down syndrome. J Neonatal Perinat Med. 2015;8(2):77–84.
81. Kamoun P. Endogenous production of hydrogen sulfide in mammals. Amino Acids. 2004;26(3):243–54.
82. Belardinelli MC, Chabli A, Chadefaux-Vekemans B, Kamoun P. Urinary sulfur compounds in down syndrome. Clin Chem. 2001;47(8):1500–1.
83. Guzmán MA, Navarro MA, Carnicer R, Sarría AJ, Acín S, Arnal C, Muniesa P, Surra JC, Arbonés-Mainar JM, Maeda N, et al. Cystathionine beta-synthase is essential for female reproductive function. Hum Mol Genet. 2006;15(21):3168–76.
84. Yang G, Wu L, Jiang B, Yang W, Qi J, Cao K, Meng Q, Mustafa AK, Mu W, Zhang S, et al. H2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. Science. 2008;322(5901):587–90.
85. Bok R, Guerra DD, Lorca RA, Wennersten SA, Harris PS, Rauniyar AK, Stabler SP, MacLean KN, Roede JR, Brown LD, et al. Cystathionine γ-lyase promotes estrogen-stimulated uterine artery blood flow via glutathione homeostasis. Redox Biol. 2021;40:101827.
86. Wang R. Physiological implications of hydrogen sulfide: a whiff exploration that blossomed. Physiol Rev. 2012;92(2):791–896.
87. Coletti R, Almeida-Pereira G, Elias LL, Antunes-Rodrigues J. Effects of hydrogen sulfide (H2S) on water intake and vasopressin and Oxytocin secretion induced by fluid deprivation. Horm Behav. 2015;67:12–20.
88. Carballal S, Cuevasanta E, Yadav PK, Gherasim C, Ballou DP, Alvarez B, Banerjee R. Kinetics of nitrite reduction and peroxynitrite formation by ferrous Heme in human cystathionine β-Synthase. J Biol Chem. 2016;291(15):8004–13.
89. Bucci M, Papapetropoulos A, Vellecco V, Zhou Z, Zaid A, Giannogonas P, Cantalupo A, Dhayade S, Karalis KP, Wang R, et al. cGMP-dependent protein kinase contributes to hydrogen sulfide-stimulated vasorelaxation. PLoS ONE. 2012;7(12):e53319.
90. Bucci M, Vellecco V, Cantalupo A, Brancaleone V, Zhou Z, Evangelista S, Calderone V, Papapetropoulos A, Cirino G. Hydrogen sulfide accounts for the peripheral vascular effects of Zofenopril independently of ACE Inhibition. Cardiovasc Res. 2014;102(1):138–47.
91. Kondo K, Bhushan S, King AL, Prabhu SD, Hamid T, Koenig S, Murohara T, Predmore BL, Gojon G Sr, Gojon G, et al. H_2S protects against pressure overload-induced heart failure via upregulation of endothelial nitric oxide synthase. Circulation. 2013;127(10):1116–27.
92. Fu M, Zhang W, Wu L, Yang G, Li H, Wang R. Hydrogen sulfide (H2S) metabolism in mitochondria and its regulatory role in energy production. Proc Natl Acad Sci U S A. 2012;109(8):2943–8.
93. Cirino G, Szabo C, Papapetropoulos A. Physiological roles of hydrogen sulfide in mammalian cells, tissues, and organs. Physiol Rev. 2023;103(1):31–276.
94. Zhao K, Li H, Li S, Yang G. Regulation of cystathionine gamma-lyase/H_2S system and its pathological implication. Front Biosci (Landmark Ed). 2014;19(8):1355–69.
95. Renga B. Hydrogen sulfide generation in mammals: the molecular biology of cystathionine-β- synthase (CBS) and cystathionine-γ-lyase (CSE). Inflamm Allergy Drug Targets. 2011;10(2):85–91.
96. Panagiotopoulos D, Andriopoulou T, Spanou VM, Droggiti DI, Gkavogianni T, Giamarellos-Bourboulis EJ, Panagopoulos P. Deficiency of hydrogen sulfide production and pregnancy rate in an experimental model: association with preterm delivery. Am J Reprod Immunol. 2023;90(3):e13764.
97. Rao SP, Dobariya P, Bellamkonda H, More SS. Role of 3-Mercaptopyruvate sulfurtransferase (3-MST) in physiology and disease. Antioxidants (Basel). 2023;12(3):603.
98. Nagahara N, Ito T, Kitamura H, Nishino T. Tissue and subcellular distribution of mercaptopyruvate sulfurtransferase in the rat: confocal laser fluorescence and Immunoelectron microscopic studies combined with biochemical analysis. Histochem Cell Biol. 1998;110(3):243–50.
99. Tomita M, Nagahara N, Ito T. Expression of 3-Mercaptopyruvate sulfurtransferase in the mouse. Molecules. 2016;21(12):1707.
100. Kabil O, Banerjee R. Redox biochemistry of hydrogen sulfide. J Biol Chem. 2010;285(29):21903–7.
101. Shibuya N, Tanaka M, Yoshida M, Ogasawara Y, Togawa T, Ishii K, Kimura H. 3-Mercaptopyruvate sulfurtransferase produces hydrogen sulfide and bound sulfane sulfur in the brain. Antioxid Redox Signal. 2009;11(4):703–14.
102. Mikami Y, Shibuya N, Kimura Y, Nagahara N, Ogasawara Y, Kimura H. Thioredoxin and Dihydrolipoic acid are required for 3-mercaptopyruvate sulfurtransferase to produce hydrogen sulfide. Biochem J. 2011;439(3):479–85.
103. Mitidieri E, Tramontano T, Gurgone D, Citi V, Calderone V, Brancaleone V, Katsouda A, Nagahara N, Papapetropoulos A, Cirino G, et al. Mercaptopyruvate acts as endogenous vasodilator independently of 3-mercaptopyruvate sulfurtransferase activity. Nitric Oxide. 2018;75:53–9.
104. Kimura Y, Koike S, Shibuya N, Lefer D, Ogasawara Y, Kimura H. 3-Mercaptopyruvate sulfurtransferase produces potential redox regulators cysteine- and glutathione-persulfide (Cys-SSH and GSSH) together with signaling molecules H(2)S(2), H(2)S(3) and H(2)S. Sci Rep. 2017;7(1):10459.

105. Nagahara N. Multiple role of 3-mercaptopyruvate sulfurtransferase: antioxidative function, H(2) S and polysulfide production and possible SO(x) production. Br J Pharmacol. 2018;175(4):577–89.
106. Shibuya N, Koike S, Tanaka M, Ishigami-Yuasa M, Kimura Y, Ogasawara Y, Fukui K, Nagahara N, Kimura H. A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells. Nat Commun. 2013;4:1366.
107. Rabus R, Venceslau SS, Wohlbrand L, Voordouw G, Wall JD, Pereira IA. A Post-Genomic view of the ecophysiology, catabolism and biotechnological relevance of Sulphate-Reducing prokaryotes. Adv Microb Physiol. 2015;66:55–321.
108. Tomasova L, Konopelski P, Ufnal M. Gut bacteria and hydrogen sulfide: the new old players in circulatory system homeostasis. Molecules. 2016;21(11):1558.
109. Kumagai H, Sejima S, Choi Y, Tanaka H, Yamada H. Crystallization and properties of cysteine desulfhydrase from aerobacter aerogenes. FEBS Lett. 1975;52(2):304–7.
110. Awano N, Wada M, Mori H, Nakamori S, Takagi H. Identification and functional analysis of Escherichia coli cysteine desulfhydrases. Appl Environ Microbiol. 2005;71(7):4149–52.
111. Blachier F, Davila AM, Mimoun S, Benetti PH, Atanasiu C, Andriamihaja M, Benamouzig R, Bouillaud F, Tomé D. Luminal sulfide and large intestine mucosa: friend or foe? Amino Acids. 2010;39(2):335–47.
112. Braccia DJ, Jiang X, Pop M, Hall AB. The capacity to produce hydrogen sulfide (H(2)S) via cysteine degradation is ubiquitous in the human gut Microbiome. Front Microbiol. 2021;12:705583.
113. Kashfi K, Olson KR. Biology and therapeutic potential of hydrogen sulfide and hydrogen sulfide-releasing chimeras. Biochem Pharmacol. 2013;85(5):689–703.
114. Benavides GA, Squadrito GL, Mills RW, Patel HD, Isbell TS, Patel RP, Darley-Usmar VM, Doeller JE, Kraus DW. Hydrogen sulfide mediates the vasoactivity of Garlic. Proc Natl Acad Sci U S A. 2007;104(46):17977–82.
115. Liang D, Wu H, Wong MW, Huang D. Diallyl trisulfide is a fast H2S donor, but Diallyl disulfide is a slow one: the reaction pathways and intermediates of glutathione with polysulfides. Org Lett. 2015;17(17):4196–9.
116. Beltowski J. Synthesis, metabolism, and signaling mechanisms of hydrogen sulfide: an overview. Methods Mol Biol. 2019;2007:1–8.
117. Yang J, Minkler P, Grove D, Wang R, Willard B, Dweik R, Hine C. Non-enzymatic hydrogen sulfide production from cysteine in blood is catalyzed by iron and vitamin B(6). Commun Biol. 2019;2:194.
118. Mulay P, Chen C, Krishna V. Enzyme-independent catabolism of cysteine with pyridoxal-5'-phosphate. Sci Rep. 2023;13(1):312.
119. Rose P, Moore PK, Whiteman M, Kirk C, Zhu YZ. Diet and hydrogen sulfide production in mammals. Antioxid Redox Signal. 2021;34(17):1378–93.
120. Magee EA, Richardson CJ, Hughes R, Cummings JH. Contribution of dietary protein to sulfide production in the large intestine: an in vitro and a controlled feeding study in humans. Am J Clin Nutr. 2000;72(6):1488–94.
121. Gao K, Wang PX, Mei X, Yang T, Yu K. Untapped potential of gut Microbiome for hypertension management. Gut Microbes. 2024;16(1):2356278.
122. Nguyen LH, Ma W, Wang DD, Cao Y, Mallick H, Gerbaba TK, Lloyd-Price J, Abu-Ali G, Hall AB, Sikavi D, et al. Association between Sulfur-Metabolizing bacterial communities in stool and risk of distal colorectal cancer in men. Gastroenterology. 2020;158(5):1313–25.
123. Murphy B, Bhattacharya R, Mukherjee P. Hydrogen sulfide signaling in mitochondria and disease. FASEB J. 2019;33(12):13098–125.
124. Jackson MR, Melideo SL, Jorns MS. Human sulfide:quinone oxidoreductase catalyzes the first step in hydrogen sulfide metabolism and produces a sulfane sulfur metabolite. Biochemistry. 2012;51(34):6804–15.
125. Módis K, Coletta C, Erdélyi K, Papapetropoulos A, Szabo C. Intramitochondrial hydrogen sulfide production by 3-mercaptopyruvate sulfurtransferase maintains mitochondrial electron flow and supports cellular bioenergetics. Faseb J. 2013;27(2):601–11.
126. Goubern M, Andriamihaja M, Nübel T, Blachier F, Bouillaud F. Sulfide, the first inorganic substrate for human cells. Faseb J. 2007;21(8):1699–706.
127. Kabil O, Banerjee R. Enzymology of H2S biogenesis, decay and signaling. Antioxid Redox Signal. 2014;20(5):770–82.
128. Tiranti V, Viscomi C, Hildebrandt T, Di Meo I, Mineri R, Tiveron C, Levitt MD, Prelle A, Fagiolari G, Rimoldi M, et al. Loss of ETHE1, a mitochondrial dioxygenase, causes fatal sulfide toxicity in ethylmalonic encephalopathy. Nat Med. 2009;15(2):200–5.
129. Sahebekhtiari N, Fernandez-Guerra P, Nochi Z, Carlsen J, Bross P, Palmfeldt J. Deficiency of the mitochondrial sulfide regulator ETHE1 disturbs cell growth, glutathione level and causes proteome alterations outside mitochondria. Biochim Biophys Acta Mol Basis Dis. 2019;1865(1):126–35.
130. Lagoutte E, Mimoun S, Andriamihaja M, Chaumontet C, Blachier F, Bouillaud F. Oxidation of hydrogen sulfide remains a priority in mammalian cells and causes reverse electron transfer in colonocytes. Biochim Biophys Acta. 2010;1797(8):1500–11.
131. Bouillaud F, Blachier F. Mitochondria and sulfide: a very old story of poisoning, feeding, and signaling? Antioxid Redox Signal. 2011;15(2):379–91.
132. Román-Morales E, Pietri R, Ramos-Santana B, Vinogradov SN, Lewis-Ballester A, López-Garriga J. Structural determinants for the formation of Sulfhemeprotein complexes. Biochem Biophys Res Commun. 2010;400(4):489–92.
133. Arbelo-López HD, Rodriguez-Mackenzie AD, Roman-Morales EM, Wymore T, López-Garriga J. Charge transfer and π to π* transitions in the visible spectra of sulfheme Met isomeric structures. J Phys Chem B. 2018;122(19):4947–55.
134. Mishanina TV, Libiad M, Banerjee R. Biogenesis of reactive sulfur species for signaling by hydrogen sulfide oxidation pathways. Nat Chem Biol. 2015;11(7):457–64.
135. Vitvitsky V, Yadav PK, Kurthen A, Banerjee R. Sulfide oxidation by a noncanonical pathway in red blood cells generates thiosulfate and polysulfides. J Biol Chem. 2015;290(13):8310–20.
136. Bostelaar T, Vitvitsky V, Kumutima J, Lewis BE, Yadav PK, Brunold TC, Filipovic M, Lehnert N, Stemmler TL, Banerjee R. Hydrogen sulfide oxidation by myoglobin. J Am Chem Soc. 2016;138(27):8476–88.
137. Sun X, Mao C, Xie Y, Zhong Q, Zhang R, Jiang D, Song Y. Therapeutic potential of hydrogen sulfide in reproductive system disorders. Biomolecules. 2024;14(5):540.
138. Boubeta FM, Bieza SA, Bringas M, Estrin DA, Boechi L, Bari SE. Mechanism of sulfide binding by ferric hemeproteins. Inorg Chem. 2018;57(13):7591–600.
139. Vitvitsky V, Yadav PK, An S, Seravalli J, Cho US, Banerjee R. Structural and mechanistic insights into Hemoglobin-catalyzed hydrogen sulfide oxidation and the fate of polysulfide products. J Biol Chem. 2017;292(13):5584–92.
140. Jensen B, Fago A. A novel possible role for Met hemoglobin as carrier of hydrogen sulfide in the blood. Antioxid Redox Signal. 2020;32(4):258–65.
141. Olson KR, Whitfield NL. Hydrogen sulfide and oxygen sensing in the cardiovascular system. Antioxid Redox Signal. 2010;12(10):1219–34.
142. Olson KR, Whitfield NL, Bearden SE, St Leger J, Nilson E, Gao Y, Madden JA. Hypoxic pulmonary vasodilation: a paradigm shift with a hydrogen sulfide mechanism. Am J Physiol Regul Integr Comp Physiol. 2010;298(1):R51–60.
143. Pandey T, Pandey V. Hydrogen sulfide (H2S) metabolism: unraveling cellular regulation, disease implications, and therapeutic prospects for precision medicine. Nitric Oxide. 2024;144:20–8.
144. Carson RJ, Konje JC. Role of hydrogen sulfide in the female reproductive tract. Expert Rev Obstet Gynecol. 2010;5:203–13.
145. Aubard Y, Darodes N, Cantaloube M. Hyperhomocysteinemia and pregnancy–review of our present Understanding and therapeutic implications. Eur J Obstet Gynecol Reprod Biol. 2000;93(2):157–65.
146. Fayed MR, Youssef M, Odah MM. Hyperhomocysteinemia is A risk marker for development of maternal pre-eclampsia. Boll Chim Farm. 2004;143(7):281–7.
147. Borisov VB, Forte E. Impact of hydrogen sulfide on mitochondrial and bacterial bioenergetics. Int J Mol Sci. 2021;22(23):12688.
148. Brosens IA. The Utero-Placental vessels at Term — the distribution and extent of physiological changes. Springer US; 1988. https://doi.org/10.1007/978-1-4615-8109-3_5.
149. Cartwright JE, Fraser R, Leslie K, Wallace AE, James JL. Remodelling at the maternal-fetal interface: relevance to human pregnancy disorders. Reproduction. 2010;140(6):803–13.
150. Zhu X, Huang Q, Jiang L, Nguyen VT, Vu T, Devlin G, Shaima J, Wang X, Chen Y, Ma L, et al. Longitudinal intravital imaging of mouse placenta. Sci Adv. 2024;10(12):eadk1278.
151. Burchell RC. Arterial blood flow into the human intervillous space. Am J Obstet Gynecol. 1967;98(3):303–11.
152. Valentin L, Sladkevicius P, Laurini R, Söderberg H, Marsal K. Uteroplacental and luteal circulation in normal first-trimester pregnancies: doppler ultrasonographic and morphologic study. Am J Obstet Gynecol. 1996;174(2):768–75.
153. Jauniaux E, Watson A, Burton G. Evaluation of respiratory gases and acid-base gradients in human fetal fluids and uteroplacental tissue between 7 and 16 weeks' gestation. Am J Obstet Gynecol. 2001;184(5):998–1003.
154. Rosenfeld CR. Distribution of cardiac output in ovine pregnancy. Am J Physiol. 1977;232(3):H231–235.
155. Palmer SK, Zamudio S, Coffin C, Parker S, Stamm E, Moore LG. Quantitative Estimation of human uterine artery blood flow and pelvic blood flow redistribution in pregnancy. Obstet Gynecol. 1992;80(6):1000–6.

Sulfatonic®

156. Roth CJ, Haeussner E, Ruebelmann T, Koch FV, Schmitz C, Frank HG, Wall WA. Dynamic modeling of uteroplacental blood flow in IUGR indicates vortices and elevated pressure in the intervillous space - a pilot study. Sci Rep. 2017;7:40771.
157. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH. Prediction of pre-eclampsia by uterine artery doppler imaging: relationship to gestational age at delivery and small-for-gestational age. Ultrasound Obstet Gynecol. 2008;31(3):310–3.
158. Wang K, Ahmad S, Cai M, Rennie J, Fujisawa T, Crispi F, Baily J, Miller MR, Cudmore M, Hadoke PW, et al. Dysregulation of hydrogen sulfide producing enzyme cystathionine γ-lyase contributes to maternal hypertension and placental abnormalities in preeclampsia. Circulation. 2013;127(25):2514–22.
159. Mohammed R, Provitera L, Cavallaro G, Lattuada D, Ercoli G, Mosca F, Villamor E. Vasomotor effects of hydrogen sulfide in human umbilical vessels. J Physiol Pharmacol. 2017;68(5):737–47.
160. Cai S, Ye Q, Zeng X, Yang G, Ye C, Chen M, Yu H, Wang Y, Wang G, Huang S, et al. CBS and MAT2A improve methionine-mediated DNA synthesis through SAMTOR/mTORC1/S6K1/CAD pathway during embryo implantation. Cell Prolif. 2021;54(1):e12950.
161. Xu JW, Gao DD, Peng L, Qiu ZE, Ke LJ, Zhu YX, Zhang YL, Zhou WL. The Gasotransmitter hydrogen sulfide inhibits transepithelial anion secretion of pregnant mouse endometrial epithelium. Nitric Oxide. 2019;90:37–46.
162. Barber A, Robson SC, Myatt L, Bulmer JN, Lyall F. Heme Oxygenase expression in human placenta and placental bed: reduced expression of placenta endothelial HO-2 in preeclampsia and fetal growth restriction. Faseb J. 2001;15(7):1158–68.
163. Cindrova-Davies T, Herrera EA, Niu Y, Kingdom J, Giussani DA, Burton GJ. Reduced cystathionine γ-lyase and increased miR-21 expression are associated with increased vascular resistance in growth-restricted pregnancies: hydrogen sulfide as a placental vasodilator. Am J Pathol. 2013;182(4):1448–58.
164. Holwerda KM, Bos EM, Rajakumar A, Ris-Stalpers C, van Pampus MG, Timmer A, Erwich JJ, Faas MM, van Goor H, Lely AT. Hydrogen sulfide producing enzymes in pregnancy and preeclampsia. Placenta. 2012;33(6):518–21.
165. Patel P, Vatish M, Heptinstall J, Wang R, Carson RJ. The endogenous production of hydrogen sulphide in intrauterine tissues. Reprod Biol Endocrinol. 2009;7:10.
166. Holwerda KM, Burke SD, Faas MM, Zsengeller Z, Stillman IE, Kang PM, van Goor H, McCurley A, Jaffe IZ, Karumanchi SA, et al. Hydrogen sulfide attenuates sFlt1-induced hypertension and renal damage by upregulating vascular endothelial growth factor. J Am Soc Nephrol. 2014;25(4):717–25.
167. Vanhaesebroeck B, Leevers SJ, Ahmadi K, Timms J, Katso R, Driscoll PC, Woscholski R, Parker PJ, Waterfield MD. Synthesis and function of 3-phosphorylated inositol lipids. Annu Rev Biochem. 2001;70:535–602.
168. Papapetropoulos A, Pyriochou A, Altaany Z, Yang G, Marazioti A, Zhou Z, Jeschke MG, Branski LK, Herndon DN, Wang R, et al. Hydrogen sulfide is an endogenous stimulator of angiogenesis. Proc Natl Acad Sci U S A. 2009;106(51):21972–7.
169. Zhou Y, Li XH, Zhang CC, Wang MJ, Xue WL, Wu DD, Ma FF, Li WW, Tao BB, Zhu YC. Hydrogen sulfide promotes angiogenesis by downregulating miR-640 via the VEGFR2/mTOR pathway. Am J Physiol Cell Physiol. 2016;310(4):C305–317.
170. You XJ, Xu C, Lu JQ, Zhu XY, Gao L, Cui XR, Li Y, Gu H, Ni X. Expression of cystathionine β-synthase and cystathionine γ-lyase in human pregnant myometrium and their roles in the control of uterine contractility. PLoS ONE. 2011;6(8):e23788.
171. Yang G, Pei Y, Cao Q, Wang R. MicroRNA-21 represses human cystathionine gamma-lyase expression by targeting at specificity protein-1 in smooth muscle cells. J Cell Physiol. 2012;227(9):3192–200.
172. Nuño-Ayala M, Guillén N, Arnal C, Lou-Bonafonte JM, de Martino A, García-de-Jalón JA, Gascón S, Osaba L, Osada J, Navarro MA. Cystathionine β-synthase deficiency causes infertility by impairing decidualization and gene expression networks in uterus implantation sites. Physiol Genomics. 2012;44(14):702–16.
173. Fisher SJ. Why is placentation abnormal in preeclampsia? Am J Obstet Gynecol. 2015;213(4 Suppl):S115–122.
174. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu. 1972;1:177–91.
175. Seok J, Jun S, Lee JO, Kim GJ. Mitochondrial dynamics in Placenta-Derived mesenchymal stem cells regulate the invasion activity of trophoblast. Int J Mol Sci. 2020;21(22):8599.
176. Seok J, Jun S, Cho J, Park S, Lee JO, Kim GJ. Human placenta-derived mesenchymal stem cells induce trophoblast invasion via dynamic effects on mitochondrial function. J Cell Physiol. 2021;236(9):6678–90.
177. Feng H, Sun Z, Han B, Xia H, Chen L, Tian C, Yan S, Shi Y, Yin J, Song W, et al. Miro2 sulfhydration by CBS/H(2)S promotes human trophoblast invasion and migration via regulating mitochondria dynamics. Cell Death Dis. 2024;15(10):776.
178. Feng H, Tian C, Jiang W, Sun Z, Li Y, Han B, Chen L, Wang D, Xiang H, Zhu J, et al. Hydrogen sulfide sustains mitochondria functions via targeting mitochondria fission regulator 1 like protein to restore human cytotrophoblast invasion and migration. Int J Biol Macromol. 2025;299:140240.
179. Chu X, Xu J, Shen X, Sheng W, Sun J, Gu Y, Lewis DF, Cooper D, Zoorob D, Wang Y. Altered production and cellular levels of hydrogen sulfide (H(2)S) in placental trophoblasts from pregnancies affected by Pre-Eclampsia. Pathophysiology. 2025;32(1):10.
180. Du J, Wang P, Gou Q, Jin S, Xue H, Li D, Tian D, Sun J, Zhang X, Teng X, et al. Hydrogen sulfide ameliorated preeclampsia via suppression of toll-like receptor 4-activated inflammation in the rostral ventrolateral medulla of rats. Biomed Pharmacother. 2022;150:113018.
181. Ramsey EM, Corner GW Jr., Donner MW. Serial and cineradioangiographic visualization of maternal circulation in the primate (hemochorial) placenta. Am J Obstet Gynecol. 1963;86:213–25.
182. Rosenfeld CR, Cornfield DN, Roy T. Ca(2+)-activated K(+) channels modulate basal and E(2)beta-induced rises in uterine blood flow in ovine pregnancy. Am J Physiol Heart Circ Physiol. 2001;281(1):H422–431.
183. Rosenfeld CR, Roy T. Large conductance Ca2+-activated and voltage-activated K+ channels contribute to the rise and maintenance of estrogen-induced uterine vasodilation and maintenance of blood pressure. Endocrinology. 2012;153(12):6012–20.
184. Lechuga TJ, Zhang HH, Sheibani L, Karim M, Jia J, Magness RR, Rosenfeld CR, Chen DB. Estrogen replacement therapy in ovariectomized nonpregnant Ewes stimulates uterine artery hydrogen sulfide biosynthesis by selectively Up-Regulating cystathionine β-Synthase expression. Endocrinology. 2015;156(6):2288–98.
185. Yong QC, Lee SW, Foo CS, Neo KL, Chen X, Bian JS. Endogenous hydrogen sulphide mediates the cardioprotection induced by ischemic postconditioning. Am J Physiol Heart Circ Physiol. 2008;295(3):H1330–40.
186. Yadav P, Chen DB, Kumar S. Region-Specific and Pregnancy-Enhanced vasodilator effects of hydrogen sulfide. Obstet Gynecol Res. 2023;6(4):309–16.
187. Mustafa AK, Gadalla MM, Sen N, Kim S, Mu W, Gazi SK, Barrow RK, Yang G, Wang R, Snyder SH. H2S signals through protein S-sulfhydration. Sci Signal. 2009;2(96):ra72.
188. Cuevasanta E, Zeida A, Carballal S, Wedmann R, Morzan UN, Trujillo M, Radi R, Estrin DA, Filipovic MR, Alvarez B. Insights into the mechanism of the reaction between hydrogen sulfide and peroxynitrite. Free Radic Biol Med. 2015;80:93–100.
189. Gao XH, Krokowski D, Guan BJ, Bederman I, Majumder M, Parisien M, Diatchenko L, Kabil O, Willard B, Banerjee R, et al. Quantitative H2S-mediated protein sulfhydration reveals metabolic reprogramming during the integrated stress response. Elife. 2015;4:e10067.
190. Saha S, Chakraborty PK, Xiong X, Dwivedi SK, Mustafi SB, Leigh NR, Ramchandran R, Mukherjee P, Bhattacharya R. Cystathionine β-synthase regulates endothelial function via protein S-sulfhydration. Faseb J. 2016;30(1):441–56.
191. Zivanovic J, Kouroussis E, Kohl JB, Adhikari B, Bursac B, Schott-Roux S, Petrovic D, Miljkovic JL, Thomas-Lopez D, Jung Y, et al. Selective persulfide detection reveals evolutionarily conserved antiaging effects of S-Sulfhydration. Cell Metab. 2019;30(6):1152–e11701113.
192. Kang M, Hashimoto A, Gade A, Akbarali HI. Interaction between hydrogen sulfide-induced sulfhydration and tyrosine nitration in the KATP channel complex. Am J Physiol Gastrointest Liver Physiol. 2015;308(6):G532–539.
193. Lorigo M, Oliveira N, Cairrao E. Clinical importance of the human umbilical artery potassium channels. Cells. 2020;9(9):1956.
194. Zhao Y, Pasanen M, Rysä J. Placental ion channels: potential target of chemical exposure. Biol Reprod. 2023;108(1):41–51.
195. Tropea T, Rigiracciolo D, Esposito M, Maggiolini M, Mandalà M. G-Protein-Coupled Estrogen receptor expression in rat uterine artery is increased by pregnancy and induces dilation in a Ca(2+) and ERK1/2 dependent manner. Int J Mol Sci. 2022;23(11):5996.
196. Corcoran JJ, Nicholson C, Sweeney M, Charnock JC, Robson SC, Westwood M, Taggart MJ. Human uterine and placental arteries exhibit tissue-specific acute responses to 17β-estradiol and estrogen-receptor-specific agonists. Mol Hum Reprod. 2014;20(5):433–41.
197. Munaron L, Avanzato D, Moccia F, Mancardi D. Hydrogen sulfide as a regulator of calcium channels. Cell Calcium. 2013;53(2):77–84.

Sulfatonic®

198. Polhemus DJ, Lefer DJ. Emergence of hydrogen sulfide as an endogenous gaseous signaling molecule in cardiovascular disease. Circ Res. 2014;114(4):730–7.
199. Ali MY, Ping CY, Mok YY, Ling L, Whiteman M, Bhatia M, Moore PK. Regulation of vascular nitric oxide in vitro and in vivo; a new role for endogenous hydrogen sulphide? Br J Pharmacol. 2006;149(6):625–34.
200. Cortese-Krott MM, Fernandez BO, Santos JL, Mergia E, Grman M, Nagy P, Kelm M, Butler A, Feelisch M. Nitrosopersulfide (SSNO(-)) accounts for sustained NO bioactivity of S-nitrosothiols following reaction with sulfide. Redox Biol. 2014;2:234–44.
201. Berenyiova A, Grman M, Mijuskovic A, Stasko A, Misak A, Nagy P, Ondriasova E, Cacanyiova S, Brezova V, Feelisch M, et al. The reaction products of sulfide and S-nitrosoglutathione are potent vasorelaxants. Nitric Oxide. 2015;46:123–30.
202. Qingyou Z, Junbao D, Weijin Z, Hui Y, Chaoshu T, Chunyu Z. Impact of hydrogen sulfide on carbon monoxide/heme Oxygenase pathway in the pathogenesis of hypoxic pulmonary hypertension. Biochem Biophys Res Commun. 2004;317(1):30–7.
203. Jin HF, Du JB, Li XH, Wang YF, Liang YF, Tang CS. Interaction between hydrogen sulfide/cystathionine gamma-lyase and carbon monoxide/heme Oxygenase pathways in aortic smooth muscle cells. Acta Pharmacol Sin. 2006;27(12):1561–6.
204. Kajimura M, Shimoyama M, Tsuyama S, Suzuki T, Kozaki S, Takenaka S, Tsubota K, Oguchi Y, Suematsu M. Visualization of gaseous monoxide reception by soluble guanylate cyclase in the rat retina. Faseb J. 2003;17(3):506–8.
205. Oreshkova T, Dimitrov R, Mourdjeva M. A cross-talk of decidual stromal cells, trophoblast, and immune cells: a prerequisite for the success of pregnancy. Am J Reprod Immunol. 2012;68(5):366–73.
206. Triggianese P, Perricone C, Chimenti MS, De Carolis C, Perricone R. Innate immune system at the Maternal-Fetal interface: mechanisms of disease and targets of therapy in pregnancy syndromes. Am J Reprod Immunol. 2016;76(4):245–57.
207. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunol Today. 1993;14(7):353–6.
208. Sun L, Chen L, Wang F, Zheng X, Yuan C, Niu Q, Li Z, Deng L, Zheng B, Li C, et al. Exogenous hydrogen sulfide prevents lipopolysaccharide-induced inflammation by blocking the TLR4/NF-κB pathway in MAC-T cells. Gene. 2019;710:114–21.
209. Wu D, Zhong P, Wang J, Wang H. Exogenous hydrogen sulfide mitigates LPS + ATP-induced inflammation by inhibiting NLRP3 inflammasome activation and promoting autophagy in L02 cells. Mol Cell Biochem. 2019;457(1–2):145–56.
210. Zhang GY, Lu D, Duan SF, Gao YR, Liu SY, Hong Y, Dong PZ, Chen YG, Li T, Wang DY, et al. Hydrogen sulfide alleviates Lipopolysaccharide-Induced diaphragm dysfunction in rats by reducing apoptosis and inflammation through ROS/MAPK and TLR4/NF-κB signaling pathways. Oxid Med Cell Longev. 2018;2018:9647809.
211. Bourque C, Zhang Y, Fu M, Racine M, Greasley A, Pei Y, Wu L, Wang R, Yang G. H(2)S protects lipopolysaccharide-induced inflammation by blocking NFκB transactivation in endothelial cells. Toxicol Appl Pharmacol. 2018;338:20–9.
212. Huang Z, Dong X, Zhuang X, Hu X, Wang L, Liao X. Exogenous hydrogen sulfide protects against high glucose–induced inflammation and cytotoxicity in H9c2 cardiac cells. Mol Med Rep. 2016;14(5):4911–7.
213. Zimmermann KK, Spassov SG, Strosing KM, Ihle PM, Engelstaedter H, Hoetzel A, Faller S. Hydrogen sulfide exerts Anti-oxidative and Anti-inflammatory effects in acute lung injury. Inflammation. 2018;41(1):249–59.
214. You X, Chen Z, Zhao H, Xu C, Liu W, Sun Q, He P, Gu H, Ni X. Endogenous hydrogen sulfide contributes to uterine quiescence during pregnancy. Reproduction. 2017;153(5):535–43.
215. Zhang J, Chen Z, Smith GN, Croy BA. Natural killer cell-triggered vascular transformation: maternal care before birth? Cell Mol Immunol. 2011;8(1):1–11.
216. Hu Y, Chen X, Pan TT, Neo KL, Lee SW, Khin ES, Moore PK, Bian JS. Cardioprotection induced by hydrogen sulfide preconditioning involves activation of ERK and PI3K/Akt pathways. Pflugers Arch. 2008;455(4):607–16.
217. Yong QC, Pan TT, Hu LF, Bian JS. Negative regulation of beta-adrenergic function by hydrogen sulphide in the rat hearts. J Mol Cell Cardiol. 2008;44(4):701–10.
218. Sen N, Paul BD, Gadalla MM, Mustafa AK, Sen T, Xu R, Kim S, Snyder SH. Hydrogen sulfide-linked sulfhydration of NF-κB mediates its antiapoptotic actions. Mol Cell. 2012;45(1):13–24.
219. Calvert JW, Jha S, Gundewar S, Elrod JW, Ramachandran A, Pattillo CB, Kevil CG, Lefer DJ. Hydrogen sulfide mediates cardioprotection through Nrf2 signaling. Circ Res. 2009;105(4):365–74.
220. Ma Q. Role of nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol Toxicol. 2013;53:401–26.
221. Fisher CD, Augustine LM, Maher JM, Nelson DM, Slitt AL, Klaassen CD, Lehman-McKeeman LD, Cherrington NJ. Induction of drug-metabolizing enzymes by Garlic and allyl sulfide compounds via activation of constitutive Androstane receptor and nuclear factor E2-related factor 2. Drug Metab Dispos. 2007;35(6):995–1000.
222. Dickhout JG, Carlisle RE, Jerome DE, Mohammed-Ali Z, Jiang H, Yang G, Mani S, Garg SK, Banerjee R, Kaufman RJ, et al. Integrated stress response modulates cellular redox state via induction of cystathionine γ-lyase: cross-talk between integrated stress response and thiol metabolism. J Biol Chem. 2012;287(10):7603–14.
223. Zhang X, Sun L. Activated PRDM1-CREBBP contributes to preeclampsia by regulating apoptosis and invasion of the human trophoblast cells. iScience. 2024;27(12):111484.
224. Zhang Y, Gao J, Sun W, Wen X, Xi Y, Wang Y, Wei C, Xu C, Li H. H(2)S restores the cardioprotective effects of ischemic post-conditioning by upregulating HB-EGF/EGFR signaling. Aging. 2019;11(6):1745–58.
225. Ni J, Jiang L, Shen G, Xia Z, Zhang L, Xu J, Feng Q, Qu H, Xu F, Li X. Hydrogen sulfide reduces pyroptosis and alleviates ischemia-reperfusion-induced acute kidney injury by inhibiting NLRP3 inflammasome. Life Sci. 2021;284:119466.
226. Xue M, Chen S, Xi J, Guan Q, Chen W, Guo Y, Chen Z. Protection against Hypoxia-Reoxygenation injury of hippocampal neurons by H(2)S via promoting phosphorylation of ROCK(2) at Tyr722 in rat model. Molecules. 2022;7(14):4567.
227. Das A, Mantena SR, Kannan A, Evans DB, Bagchi MK, Bagchi IC. De Novo synthesis of Estrogen in pregnant uterus is critical for stromal decidualization and angiogenesis. Proc Natl Acad Sci U S A. 2009;106(30):12542–7.
228. Malassiné A, Frendo JL, Evain-Brion D. A comparison of placental development and endocrine functions between the human and mouse model. Hum Reprod Update. 2003;9(6):531–9.
229. Mesiano S. Endocrinology of human pregnancy and Fetal-Placental neuroendocrine development. Yen Jaffe's Reproductive Endocrinol (Eighth Edition). 2019:256–84. https://doi.org/10.1016/B978-1-4160-4907-4.00011-5.
230. Costa MA. The endocrine function of human placenta: an overview. Reprod Biomed Online. 2016;32(1):14–43.
231. Peter M, Dörr HG, Sippell WG. Changes in the concentrations of dehydroepiandrosterone sulfate and estriol in maternal plasma during pregnancy: a longitudinal study in healthy women throughout gestation and at term. Horm Res. 1994;42(6):278–81.
232. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev. 2011;32(1):81–151.
233. Thomas MP, Potter BV. The structural biology of oestrogen metabolism. J Steroid Biochem Mol Biol. 2013;137:27–49.
234. Falah N, Torday J, Quinney S, Haas D. Estriol review: Clinical applications and potential biomedical importance. 2015.
235. Gérard C, Arnal JF, Jost M, Douxfils J, Lenfant F, Fontaine C, Houtman R, Archer DF, Reid RL, Lobo RA, et al. Profile of estetrol, a promising native Estrogen for oral contraception and the relief of climacteric symptoms of menopause. Expert Rev Clin Pharmacol. 2022;15(2):121–37.
236. Holinka CF, Diczfalusy E, Coelingh Bennink HJ. Estetrol: a unique steroid in human pregnancy. J Steroid Biochem Mol Biol. 2008;110(1–2):138–43.
237. Oakey RE. The progressive increase in Estrogen production in human pregnancy: an appraisal of the factors responsible. Vitam Horm. 1970;28:1–36.
238. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies. Obstet Gynecol. 2009;114(6):1326–31.
239. Reynolds LP, Redmer DA. Utero-placental vascular development and placental function. J Anim Sci. 1995;73(6):1839–51.
240. Reynolds LP, Kirsch JD, Kraft KC, Knutson DL, McClaflin WJ, Redmer DA. Time-course of the uterine response to estradiol-17beta in ovariectomized ewes: uterine growth and microvascular development. Biol Reprod. 1998;59(3):606–12.
241. Albrecht ED, Pepe GJ. Placental steroid hormone biosynthesis in primate pregnancy. Endocr Rev. 1990;11(1):124–50.
242. Carnegie JA, Robertson HA. Conjugated and unconjugated estrogens in fetal and maternal fluids of the pregnant ewe: a possible role for estrone sulfate during early pregnancy. Biol Reprod. 1978;19(1):202–11.

Sulfatonic®

243. Ford SP. Control of uterine and ovarian blood flow throughout the estrous cycle and pregnancy of ewes, sows and cows. J Anim Sci. 1982;55(Suppl 2):32–42.
244. Koritke JG, Gillet JY, Muller P. [The microvascularization of vaginal mucosa and its variations during the ovarian cycle women]. Z Zellforsch Mikrosk Anat. 1969;99(1):37–53.
245. Magness RR, Rosenfeld CR, Carr BR. Protein kinase C in uterine and systemic arteries during ovarian cycle and pregnancy. Am J Physiol. 1991;260(3 Pt 1):E464–470.
246. Magness RR, Rosenfeld CR. Local and systemic estradiol-17 beta: effects on uterine and systemic vasodilation. Am J Physiol. 1989;256(4 Pt 1):E536–542.
247. Martini PG, Katzenellenbogen BS. Modulation of Estrogen receptor activity by selective coregulators. J Steroid Biochem Mol Biol. 2003;85(2–5):117–22.
248. Driscoll MD, Sathya G, Muyan M, Klinge CM, Hilf R, Bambara RA. Sequence requirements for Estrogen receptor binding to Estrogen response elements. J Biol Chem. 1998;273(45):29321–30.
249. Chang K, Lubo Z. Review article: steroid hormones and uterine vascular adaptation to pregnancy. Reprod Sci. 2008;15(4):336–48.
250. Orimo A, Inoue S, Ikegami A, Hosoi T, Akishita M, Ouchi Y, Muramatsu M, Orimo H. Vascular smooth muscle cells as target for Estrogen. Biochem Biophys Res Commun. 1993;195(2):730–6.
251. Rosenfeld CR, Cox BE, Roy T, Magness RR. Nitric oxide contributes to estrogen-induced vasodilation of the ovine uterine circulation. J Clin Invest. 1996;98(9):2158–66.
252. Chen DB, Bird IM, Zheng J, Magness RR. Membrane Estrogen receptor-dependent extracellular signal-regulated kinase pathway mediates acute activation of endothelial nitric oxide synthase by Estrogen in uterine artery endothelial cells. Endocrinology. 2004;145(1):113–25.
253. Silva de Sá MF, Meirelles RS. Vasodilating effect of Estrogen on the human umbilical artery. Gynecol Invest. 1977;8(5–6):307–13.
254. Leiberman JR, Wiznitzer A, Glezerman M, Feldman B, Levy J, Sharoni Y. Estrogen and progesterone receptors in the uterine artery of rats during and after pregnancy. Eur J Obstet Gynecol Reprod Biol. 1993;51(1):35–40.
255. Jiang CW, Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P. Endothelium-independent relaxation of rabbit coronary artery by 17 beta-oestradiol in vitro. Br J Pharmacol. 1991;104(4):1033–7.
256. Mügge A, Riedel M, Barton M, Kuhn M, Lichtlen PR. Endothelium independent relaxation of human coronary arteries by 17 beta-oestradiol in vitro. Cardiovasc Res. 1993;27(11):1939–42.
257. Kublickiene KR, Kublickas M, Lindblom B, Lunell NO, Nisell H. A comparison of myogenic and endothelial properties of myometrial and omental resistance vessels in late pregnancy. Am J Obstet Gynecol. 1997;176(3):560–6.
258. Stice SL, Ford SP, Rosazza JP, Van Orden DE. Interaction of 4-hydroxylated estradiol and potential-sensitive Ca2 + channels in altering uterine blood flow during the estrous cycle and early pregnancy in gilts. Biol Reprod. 1987;36(2):369–75.
259. Khan LH, Rosenfeld CR, Liu XT, Magness RR. Regulation of the cGMP-cPKG pathway and large-conductance Ca2+-activated K + channels in uterine arteries during the ovine ovarian cycle. Am J Physiol Endocrinol Metab. 2010;298(2):E222–228.
260. Rosenfeld CR, Roy T, Cox BE. Mechanisms modulating estrogen-induced uterine vasodilation. Vascul Pharmacol. 2002;38(2):115–25.
261. White RE, Darkow DJ, Lang JL. Estrogen relaxes coronary arteries by opening BKCa channels through a cGMP-dependent mechanism. Circ Res. 1995;77(5):936–42.
262. Terragno NA, Terragno DA, Pacholczyk D, McGiff JC. Prostaglandins and the regulation of uterine blood flow in pregnancy. Nature. 1974;249(452):57–8.
263. Burger NZ, Kuzina OY, Osol G, Gokina NI. Estrogen replacement enhances EDHF-mediated vasodilation of mesenteric and uterine resistance arteries: role of endothelial cell Ca2+. Am J Physiol Endocrinol Metab. 2009;296(3):E503–512.
264. Rusidzé M, Gargaros A, Fébrissy C, Dubucs C, Weyl A, Ousselin J, Aziza J, Arnal JF, Lenfant F. Estrogen actions in placental vascular morphogenesis and spiral artery remodeling: A comparative view between humans and mice. Cells. 2023;12(4):620.
265. Bukovsky A, Caudle MR, Cekanova M, Fernando RI, Wimalasena J, Foster JS, Henley DC, Elder RF. Placental expression of Estrogen receptor beta and its hormone binding variant–comparison with Estrogen receptor alpha and a role for Estrogen receptors in asymmetric division and differentiation of Estrogen-dependent cells. Reprod Biol Endocrinol. 2003;1:36.
266. Kumar P, Kamat A, Mendelson CR. Estrogen receptor alpha (ERalpha) mediates stimulatory effects of Estrogen on aromatase (CYP19) gene expression in human placenta. Mol Endocrinol. 2009;23(6):784–93.
267. Schiessl B, Mylonas I, Hantschmann P, Kuhn C, Schulze S, Kunze S, Friese K, Jeschke U. Expression of endothelial NO synthase, inducible NO synthase, and Estrogen receptors alpha and beta in placental tissue of normal, preeclamptic, and intrauterine growth-restricted pregnancies. J Histochem Cytochem. 2005;53(12):1441–9.
268. Patel S, Kilburn B, Imudia A, Armant DR, Skafar DF. Estradiol elicits proapoptotic and antiproliferative effects in human trophoblast cells. Biol Reprod. 2015;93(3):74.
269. Kuiper GG, Carlsson B, Grandien K, Enmark E, Häggblad J, Nilsson S, Gustafsson JA. Comparison of the ligand binding specificity and transcript tissue distribution of Estrogen receptors alpha and beta. Endocrinology. 1997;138(3):863–70.
270. Pfaffl MW, Lange IG, Daxenberger A, Meyer HH. Tissue-specific expression pattern of Estrogen receptors (ER): quantification of ER alpha and ER beta mRNA with real-time RT-PCR. Apmis. 2001;109(5):345–55.
271. Nelson ER, Habibi HR. Estrogen receptor function and regulation in fish and other vertebrates. Gen Comp Endocrinol. 2013;192:15–24.
272. Batra S, Iosif S. Nuclear Estrogen receptors in human uterine arteries. Gynecol Obstet Invest. 1987;24(4):250–5.
273. Wu WX, Ma XH, Smith GC, Nathanielsz PW. Differential distribution of ERalpha and erbeta mRNA in intrauterine tissues of the pregnant rhesus monkey. Am J Physiol Cell Physiol. 2000;278(1):C190–198.
274. Lechuga TJ, Bilg AK, Patel BA, Nguyen NA, Qi QR, Chen DB. Estradiol-17β stimulates H(2) S biosynthesis by ER-dependent CBS and CSE transcription in uterine artery smooth muscle cells in vitro. J Cell Physiol. 2019;234(6):9264–73.
275. Bai J, Lechuga TJ, Makhoul J, Yan H, Major C, Hameed A, Chen DB. ERα/ERβ-directed CBS transcription mediates E2β-stimulated hUAEC H2S production. J Mol Endocrinol. 2023;70(2):e220175.
276. Bai J, Chen DB. Enhanced Sp1/YY1 expression directs CBS transcription to mediate VEGF-Stimulated Pregnancy-Dependent H(2)S production in human uterine artery endothelial cells. Hypertension. 2021;78(6):1902–13.
277. Safe S. Transcriptional activation of genes by 17 beta-estradiol through Estrogen receptor-Sp1 interactions. Vitam Horm. 2001;62:231–52.
278. Xu X, Yan Q, Liu X, Li P, Li X, Chen Y, Simoncini T, Liu J, Zhu D, Fu X. 17β-Estradiol nongenomically induces vascular endothelial H(2)S release by promoting phosphorylation of cystathionine γ-lyase. J Biol Chem. 2019;294(43):15577–92.
279. d'Emmanuele di Villa, Bianca R, Mitidieri E, Fusco F, Russo A, Pagliara V, Tramontano T, Donnarumma E, Mirone V, Cirino G, Russo G, et al. Urothelium muscarinic activation phosphorylates CBS(Ser227) via cGMP/PKG pathway causing human bladder relaxation through H2S production. Sci Rep. 2016;6:31491.
280. Barton M, Meyer MR. Postmenopausal hypertension: mechanisms and therapy. Hypertension. 2009;54(1):11–8.
281. Fiorucci S, Distrutti E, Cirino G, Wallace JL. The emerging roles of hydrogen sulfide in the Gastrointestinal tract and liver. Gastroenterology. 2006;131(1):259–71.
282. Marutani E, Yamada M, Ida T, Tokuda K, Ikeda K, Kai S, Shirozu K, Hayashida K, Kosugi S, Hanaoka K, et al. Thiosulfate mediates cytoprotective effects of hydrogen sulfide against neuronal ischemia. J Am Heart Assoc. 2015;4(11):e002125.
283. Olson KR. The therapeutic potential of hydrogen sulfide: separating hype from hope. Am J Physiol Regul Integr Comp Physiol. 2011;301(2):R297–312.
284. Kang J, Li Z, Organ CL, Park CM, Yang CT, Pacheco A, Wang D, Lefer DJ, Xian M. pH-Controlled hydrogen sulfide release for myocardial Ischemia-Reperfusion injury. J Am Chem Soc. 2016;138(20):6336–9.
285. Wang M, Tang J, Zhang S, Pang K, Zhao Y, Liu N, Huang J, Kang J, Dong S, Li H, et al. Exogenous H(2)S initiating Nrf2/GPx4/GSH pathway through promoting Syvn1-Keap1 interaction in diabetic hearts. Cell Death Discov. 2023;9(1):394.
286. Li L, Whiteman M, Guan YY, Neo KL, Cheng Y, Lee SW, Zhao Y, Baskar R, Tan CH, Moore PK. Characterization of a novel, water-soluble hydrogen sulfide-releasing molecule (GYY4137): new insights into the biology of hydrogen sulfide. Circulation. 2008;117(18):2351–60.
287. Rose P, Dymock BW, Moore PK. GYY4137, a novel water-soluble, H2S-releasing molecule. Methods Enzymol. 2015;554:143–67.
288. Whiteman M, Perry A, Zhou Z, Bucci M, Papapetropoulos A, Cirino G, Wood ME. Phosphinodithioate and phosphoramidodithioate hydrogen sulfide donors. Handb Exp Pharmacol. 2015;230:337–63.

Sulfatonic®

289. Cao Y, Adhikari S, Ang AD, Moore PK, Bhatia M. Mechanism of induction of pancreatic acinar cell apoptosis by hydrogen sulfide. Am J Physiol Cell Physiol. 2006;291(3):C503–510.
290. Wang Q, Liu HR, Mu Q, Rose P, Zhu YZ. S-propargyl-cysteine protects both adult rat hearts and neonatal cardiomyocytes from ischemia/hypoxia injury: the contribution of the hydrogen sulfide-mediated pathway. J Cardiovasc Pharmacol. 2009;54(2):139–46.
291. Rong F, Bao W, Li G, Ge Y, Zhu W, Hao B, Zhao Y, Yuan Y, Wang Y. Aminopeptidase N-Activated Self-immolative hydrogen sulfide donor for inflammatory Response-Specific wound healing. Angew Chem Int Ed Engl. 2025;64(14):e202423527. https://doi.org/10.1002/anie.202423527.
292. Liu L, Yao Y, Liu Y, Hong B, Li Z, Chen X, Zhang Y, Fu H, Yang D, Yang C. Targeted H(2)S-Mediated gas therapy with pH-Sensitive release property for myocardial Ischemia-Reperfusion injury by platelet membrane. Biomater Res. 2024;28:0061.
293. Raggio R, Bonani W, Callone E, Dirè S, Gambari L, Grassi F, Motta A. Silk fibroin porous scaffolds loaded with a Slow-Releasing hydrogen sulfide agent (GYY4137) for applications of tissue engineering. ACS Biomater Sci Eng. 2018;4(8):2956–66.
294. Zhao Y, Biggs TD, Xian M. Hydrogen sulfide (H2S) releasing agents: chemistry and biological applications. Chem Commun (Camb). 2014;50(80):11788–805.
295. Szabo C, Papapetropoulos A. International union of basic and clinical pharmacology. CII: Pharmacological modulation of H(2)S levels: H(2)S donors and H(2)S biosynthesis inhibitors. Pharmacol Rev. 2017;69(4):497–564.
296. Högberg U. The world health report 2005: make every mother and child count - including Africans. Scand J Public Health. 2005;33(6):409–11.
297. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785–99.
298. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, McAuliffe F, da Silva Costa F, von Dadelszen P, McIntyre HD, et al. The international federation of gynecology and obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019;145(Suppl 1Suppl 1):1–33.
299. Hu TX, Guo X, Wang G, Gao L, He P, Xia Y, Gu H, Ni X. MiR133b is involved in endogenous hydrogen sulfide suppression of sFlt-1 production in human placenta. Placenta. 2017;52:33–40.
300. Yadav P, Mishra JS, Hurt MW, Chen DB, Kumar S. H2S donor GYY4137 mitigates sFlt-1-induced hypertension and vascular dysfunction in pregnant rats†. Biol Reprod. 2024;111(4):879–89.
301. Rezai H, Ahmad S, Alzahrani FA, Sanchez-Aranguren L, Dias IH, Agrawal S, Sparatore A, Wang K, Ahmed A. MZe786, a hydrogen sulfide-releasing aspirin prevents preeclampsia in Heme oxygenase-1 haplodeficient pregnancy under high soluble flt-1 environment. Redox Biol. 2021;38:101768.
302. Wang X, Yu S, Jian Y, Pan H, Guo J, Wu J, Guo W. Hydrogen sulfide against preeclampsia exposure-induced oxidative mitochondrial damage in HTR-8/SVneo cells. Front Cardiovasc Med. 2022;9:1023982.
303. Zhang C, Chen Z, Shao H, Ma Z, Guan R, Yu X, Sun Q, Gu H. Exogenous hydrogen sulfide prevents necroptosis by inhibiting p38MAPK pathway activation in JEG-3 trophoblast cells: A role in preeclampsia. Gynecol Obstet Invest. 2024;89(5):387–401.
304. Saxena S, John BA, Verma N, Mishra M. The dysregulation of microRNA-30b directly regulates cystathionine Gamma-Lyase and exhibits poor invasion activity in preeclampsia. Cureus. 2025;17(1):e78036.
305. Zhang H, Huang Y, Chen S, Tang C, Wang G, Du J, Jin H. Hydrogen sulfide regulates insulin secretion and insulin resistance in diabetes mellitus, a new promising target for diabetes mellitus treatment? A review. J Adv Res. 2021;27:19–30.
306. Tang C, Li X, Du J. Hydrogen sulfide as a new endogenous gaseous transmitter in the cardiovascular system. Curr Vasc Pharmacol. 2006;4(1):17–22.
307. Liu YH, Lu M, Hu LF, Wong PT, Webb GD, Bian JS. Hydrogen sulfide in the mammalian cardiovascular system. Antioxid Redox Signal. 2012;17(1):141–85.
308. Kimura H. The physiological role of hydrogen sulfide and beyond. Nitric Oxide. 2014;41:4–10.
309. Szabo C. Roles of hydrogen sulfide in the pathogenesis of diabetes mellitus and its complications. Antioxid Redox Signal. 2012;17(1):68–80.
310. Szabó C. Hydrogen sulphide and its therapeutic potential. Nat Rev Drug Discov. 2007;6(11):917–35.
311. Jain SK, Bull R, Rains JL, Bass PF, Levine SN, Reddy S, McVie R, Bocchini JA. Low levels of hydrogen sulfide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? Antioxid Redox Signal. 2010;12(11):1333–7.
312. Whiteman M, Gooding KM, Whatmore JL, Ball CI, Mawson D, Skinner K, Tooke JE, Shore AC. Adiposity is a major determinant of plasma levels of the novel vasodilator hydrogen sulphide. Diabetologia. 2010;53(8):1722–6.
313. Suzuki K, Sagara M, Aoki C, Tanaka S, Aso Y. Clinical implication of plasma hydrogen sulfide levels in Japanese patients with type 2 diabetes. Intern Med. 2017;56(1):17–21.
314. Okamoto M, Yamaoka M, Takei M, Ando T, Taniguchi S, Ishii I, Tohya K, Ishizaki T, Niki I, Kimura T. Endogenous hydrogen sulfide protects pancreatic beta-cells from a high-fat diet-induced glucotoxicity and prevents the development of type 2 diabetes. Biochem Biophys Res Commun. 2013;442(3–4):227–33.
315. Zhang J, Chi H, Xiao H, Tian X, Wang Y, Yun X, Xu Y. Interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) single nucleotide polymorphisms (SNPs), inflammation and metabolism in gestational diabetes mellitus in inner Mongolia. Med Sci Monit. 2017;23:4149–57.
316. Pichette J, Fynn-Sackey N, Gagnon J. Hydrogen sulfide and sulfate prebiotic stimulates the secretion of GLP-1 and improves glycemia in male mice. Endocrinology. 2017;158(10):3416–25.
317. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primers. 2019;5(1):47.
318. Hivert MF, Backman H, Benhalima K, Catalano P, Desoye G, Immanuel J, McKinlay CJD, Meek CL, Nolan CJ, Ram U, et al. Pathophysiology from preconception, during pregnancy, and beyond. Lancet. 2024;404(10448):158–74.
319. Egidy Assenza G, Dimopoulos K, Budts W, Donti A, Economy KE, Gargiulo GD, Gatzoulis M, Landzberg MJ, Valente AM, Roos-Hesselink J. Management of acute cardiovascular complications in pregnancy. Eur Heart J. 2021;42(41):4224–40.
320. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ. 2020;369:m1361.
321. Teng Y, Xuan S, Jiang M, Tian L, Tian J, Chang Q. Expression of H(2)S in gestational diabetes mellitus and correlation analysis with inflammatory markers IL-6 and TNF-α. J Diabetes Res. 2020;2020:3085840.
322. John CM, Mohamed Yusof NIS, Abdul Aziz SH, Mohd Fauzi F. Maternal cognitive impairment associated with gestational diabetes Mellitus-A review of potential contributing mechanisms. Int J Mol Sci. 2018;19(12):3894.
323. Liu T, Deng JM, Liu YL, Chang L, Jiang YM. The relationship between gestational diabetes mellitus and Interleukin 1beta gene polymorphisms in Southwest of China. Med (Baltim). 2020;99(43):e22679.
324. Fatima SS, Alam F, Chaudhry B, Khan TA. Elevated levels of chemerin, leptin, and interleukin-18 in gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2017;30(9):1023–8.
325. Gomes CP, Torloni MR, Gueuvoghlanian-Silva BY, Alexandre SM, Mattar R, Daher S. Cytokine levels in gestational diabetes mellitus: a systematic review of the literature. Am J Reprod Immunol. 2013;69(6):545–57.
326. Zhou F, Li C, Zhang SY. NLRP3 inflammasome: a new therapeutic target for high-risk reproductive disorders? Chin Med J (Engl). 2020;134(1):20–7.
327. Fang X, Wang Y, Zhang Y, Li Y, Kwak-Kim J, Wu L. NLRP3 inflammasome and its critical role in gynecological disorders and obstetrical complications. Front Immunol. 2020;11:555826.
328. Zhang R, Zhang X, Xing B, Zhao J, Zhang P, Shi D, Yang F. Astragaloside IV attenuates gestational diabetes mellitus via targeting NLRP3 inflammasome in genetic mice. Reprod Biol Endocrinol. 2019;17(1):77.
329. Wu W, Tan QY, Xi FF, Ruan Y, Wang J, Luo Q, Dou XB, Hu TX. NLRP3 inflammasome activation in gestational diabetes mellitus placentas is associated with hydrogen sulfide synthetase deficiency. Exp Ther Med. 2022;23(1):94.
330. Chen CQ, Xin H, Zhu YZ. Hydrogen sulfide: third gaseous transmitter, but with great Pharmacological potential. Acta Pharmacol Sin. 2007;28(11):1709–16.
331. Simpson S, Smith L, Bowe J. Placental peptides regulating islet adaptation to pregnancy: clinical potential in gestational diabetes mellitus. Curr Opin Pharmacol. 2018;43:59–65.
332. Hill DJ. Placental control of metabolic adaptations in the mother for an optimal pregnancy outcome. What goes wrong in gestational diabetes? Placenta. 2018;69:162–8.
333. Chen Z, Zhang M, Zhao Y, Xu W, Xiang F, Li X, Zhang T, Wu R, Kang X. Hydrogen sulfide contributes to uterine quiescence through Inhibition of NLRP3 inflammasome activation by suppressing the TLR4/NF-κB signalling pathway. J Inflamm Res. 2021;14:2753–68.
334. Liu W, Xu C, You X, Olson DM, Chemtob S, Gao L, Ni X. Hydrogen sulfide delays LPS-Induced preterm birth in mice via Anti-Inflammatory pathways. PLoS ONE. 2016;11(4):e0152838.

335. Sidhu R, Singh M, Samir G, Carson RJ. L-cysteine and sodium hydrosulphide inhibit spontaneous contractility in isolated pregnant rat uterine strips in vitro. Pharmacol Toxicol. 2001;88(4):198–203.
336. Hu R, Lu J, You X, Zhu X, Hui N, Ni X. Hydrogen sulfide inhibits the spontaneous and oxytocin-induced contractility of human pregnant myometrium. Gynecol Endocrinol. 2011;27(11):900–4.
337. Robinson H, Wray S. A new slow releasing, H_2S generating compound, GYY4137 relaxes spontaneous and oxytocin-stimulated contractions of human and rat pregnant myometrium. PLoS ONE. 2012;7(9):e46278.
338. Mijušković A, Kokić AN, Dušić ZO, Slavić M, Spasić MB, Blagojević D. Chloride channels mediate sodium sulphide-induced relaxation in rat Uteri. Br J Pharmacol. 2015;172(14):3671–86.
339. Mijušković A, Wray S, Arrowsmith S. A hydrogen sulphide-releasing non-steroidal anti-inflammatory, ATB-346, significantly attenuates human myometrial contractions. Pharmacol Rep. 2025;77(1):287–94.
340. Crosignani PG, Rubin BL. Recurrent spontaneous abortion. Hum Reprod. 1991;6(4):609–10.
341. Coulam CB, Clark DA, Beer AE, Kutteh WH, Silver R, Kwak J, Stephenson M. Current clinical options for diagnosis and treatment of recurrent spontaneous abortion. Clinical guidelines recommendation committee for diagnosis and treatment of recurrent spontaneous abortion. Am J Reprod Immunol. 1997;38(2):57–74.
342. Raghupathy R. Th1-type immunity is incompatible with successful pregnancy. Immunol Today. 1997;18(10):478–82.
343. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertil Steril. 2010;93(4):1234–43.
344. Hill JA, Polgar K, Anderson DJ. T-helper 1-type immunity to trophoblast in women with recurrent spontaneous abortion. JAMA. 1995;273(24):1933–6.
345. La Rocca C, Carbone F, Longobardi S, Matarese G. The immunology of pregnancy: regulatory T cells control maternal immune tolerance toward the fetus. Immunol Lett. 2014;162(1 Pt A):41–8.
346. Yang R, Qu C, Zhou Y, Konkel JE, Shi S, Liu Y, Chen C, Liu S, Liu D, Chen Y, et al. Hydrogen sulfide promotes Tet1- and Tet2-Mediated Foxp3 demethylation to drive regulatory T cell differentiation and maintain immune homeostasis. Immunity. 2015;43(2):251–63.
347. Velicky P, Knöfler M, Pollheimer J. Function and control of human invasive trophoblast subtypes: intrinsic vs. maternal control. Cell Adh Migr. 2016;10(1–2):154–62.
348. Fetal Growth Restriction. ACOG practice bulletin, number 227. Obstet Gynecol. 2021;137(2):e16–28.
349. Arbeille P. Fetal arterial Doppler-IUGR and hypoxia. Eur J Obstet Gynecol Reprod Biol. 1997;75(1):51–3.
350. Sun C, Groom KM, Oyston C, Chamley LW, Clark AR, James JL. The placenta in fetal growth restriction: what is going wrong? Placenta. 2020;96:10–8.
351. Lu L, Kingdom J, Burton GJ, Cindrova-Davies T. Placental stem villus arterial remodeling associated with reduced hydrogen sulfide synthesis contributes to human fetal growth restriction. Am J Pathol. 2017;187(4):908–20.
352. Zochio GP, Possomato-Vieira JS, Chimini JS, da Silva MLS, Dias-Junior CA. Effects of fast versus slow-releasing hydrogen sulfide donors in hypertension in pregnancy and fetoplacental growth restriction. Naunyn Schmiedebergs Arch Pharmacol. 2019;392(12):1561–8.
353. Bai Z, Zhang J, Zhang Q, Zhang T, Li J, Zhao Q, Wang Z, He D, Cheng J, Zhang J. Synthesis, toxicities and bio-activities of manganese complexes with CO and H 2 S dual donors. Eur J Med Chem. 2018;159:339–56.
354. Wang XL, Wang ZY, Ling JJ, Zhang YH, Yin J. Synthesis and biological evaluation of nitric oxide (NO)-hydrogen sulfide (H(2)S) releasing derivatives of (S)-3-n-butylphthalide as potential antiplatelet agents. Chin J Nat Med. 2016;14(12):946–53.
355. Kodela R, Chattopadhyay M, Kashfi K. NOSH-Aspirin: A novel nitric Oxide-Hydrogen Sulfide-Releasing hybrid: A new class of Anti-inflammatory pharmaceuticals. ACS Med Chem Lett. 2012;3(3):257–62.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Sulfatonic®